Stereoselective construction of quaternary centres under Brønsted acid catalysis

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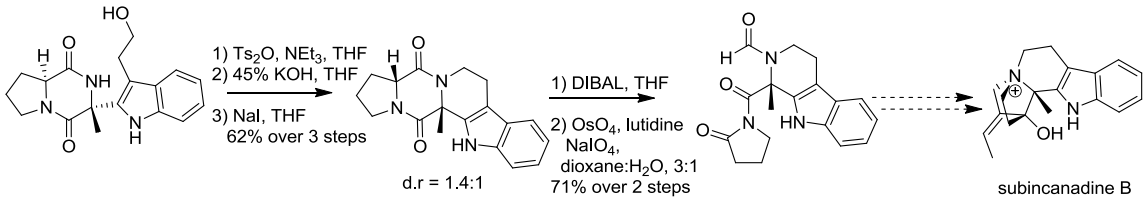
The University of Manchester Chloe Holloway

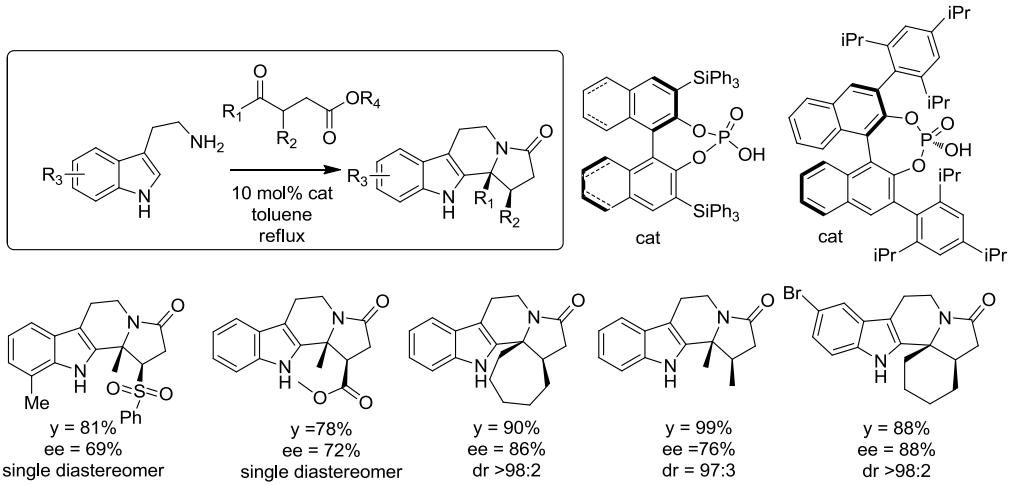
Stereoselective construction of quaternary centres under Brønsted acid catalysis

For the degree of 'Doctor of Philosophy' 2010

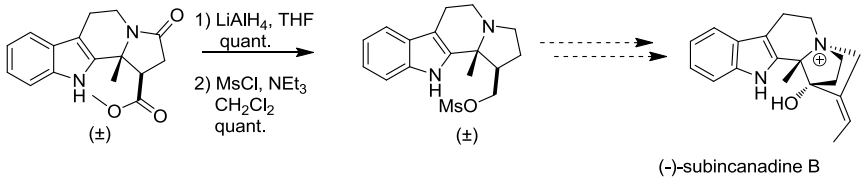
A methodology featuring the diastereoselective addition of tryptamine derivatives to a proline derived diketopiperazine in the presence of an achiral Brønsted acid catalyst was used in the synthetic studies towards Subincanadine B, an indole alkaloid natural product. The synthesis began with the formation of a fused pentacyclic intermediate containing a diketopiperazine moiety. Cleavage of the diketopiperazine was required to proceed with the synthesis but this did not prove facile. It was possible to cleave the least hindered amide bond of the diketopiperazine, but attempts to cleave both amide bonds were unsuccessful.



A new methodology to access subincanadine B was developed. This featured an asymmetric Pictet-Spengler reaction catalysed by a BINOL-derived phosphoric acid catalyst. Differently substituted tryptamines were reacted with various 1,4-dicarbonyl compounds bearing a variety of functional groups α-to the ketone in the presence of a chiral phosphoric acid catalyst. A range of products were obtained in excellent yield and diastereoselectivity, and in moderate to high enantiomeric excess.



This methodology was used in a further attempt to access subincanadine B. The Pictet-Spengler cyclisation product with a methyl ester adjacent to the chiral quaternary centre was used as the starting material in the synthesis. Using this methodology, an advanced tetracyclic intermediate was successfully synthesised. Further studies are currently being aimed at completing the synthesis.



Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. All compounds synthesised by myself are shown in the Experimental section but data for compounds synthesised by other colleagues are not reported. All the compounds in this thesis are racemic unless otherwise drawn. The relative stereochemistry of the compounds is not defined unless otherwise stated. Initial studies into the enantioselective Pictet-Spengler cyclisation reaction using phosphoric acid catalysis were conducted by Michael Muratore. The phosphoric acid catalysts used were obtained from commercial sources or synthesised by Michael Muratore. The term 'single diastereomer' is used for compounds where the minor diastereomer was not visible in the crude ^{1}H NMR spectrum. The absolute configuration was determined for compounds characterised by x-ray crystallography only where the Flack parameter was < 0.04 in magnitude. For compounds (**2.54**), (**2.55**) and (**2.62**), the x-rays were used to determine the relative stereochemistry and the absolute stereochemistry could be assigned from the fixed stereocentre of L-proline. Only the relative stereochemistry could be assigned for compound (**4.167**) using x-ray crystallography.

Chloe Holloway December 2010

Copyright Statement

Acknowledgements

I'm glad to have completed my PhD which would not have been possible without the guidance and support of my supervisor, friends and family.

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Abbreviations

ºC	degrees Celsius
$[\alpha]_D$	optical rotation
Å	angstrom
Ac	acetyl
acac	acetylacetonate
app	apparent
aq	aqueous
Ar	aromatic
BHT	butylated hydroxytoluene
BINOL	1,1'-binaphthalene-2,2'-diol
Bn	benzyl
Boc	*tert*-butyloxy carbonyl
Bu	butyl
c	concentration
cat	catalyst
Cbz	benzyloxy carbonyl
CDI	1,1'-carbonyldiimidazole
*m*CPBA	*meta*-chloroperoxybenzoic acid
CI	chemical ionization
d	doublet
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
de	diastereomeric excess
DKP	diketopiperazine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N,N'*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
DYKAT	dynamic kinetic asymmetric transformation
E	electrophile
ee	enantiomeric excess
ES	electrospray
Et	ethyl
EWG	electron withdrawing group
g	gram
Hetaryl	heteroaryl group
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
hr	hour(s)
HRMS	high resolution mass spectrum
i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IR	infra-red
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
m	multiplet
M	molar
Me	methyl
MEM	methoxyethoxymethyl ether
Mes	mesityl (2,4,6-trimethylbenzene)
mg	milligram
min	minute
mL	millilitre
mmol	millimole

mol	mole
MMPP	magnesium monoperoxyphthalate
M.P.	melting point
MS	molecular sieves
Ms	methanesulfonyl
m/z	mass/charge ratio
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
Ns	nosyl (4-nitrobenzenesulfonyl)
o	ortho
P	any protecting group
p	para
PA	phosphoric acid
PCC	pyridinium chlorochromate
Ph	phenyl
pH	negative log of the concentration of protons in water
Phth	phthalic anhydride
Piv	pivaloyl
pKa	negative log to the base ten of the acid dissociation constant
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
Py	pyridine
q	quartet
quant	quantitative
R	any functional group
R_f	retention factor
Ra-Ni	Raney nickel
rt	room temperature
s	singlet
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
S_N2	bimolecular nucleophilic substitution
t	tertiary
t	triplet
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
unsubst	unsubstituted
VAPOL	2,2'-diphenyl-3,3'-(4-biphenanthrol)
v_{max}	frequency maxima

Chapter 1: Overview

1.1 Organocatalysis

The field of organocatalysis[1] has grown exponentially in the last decade since David Macmillan coined the term in 2000[2] (Figure 1.1). The interest of numerous research groups in the field and their development of a wide range of organocatalysts suggests that organocatalysis has become favoured over traditional transition metal catalysis in a number of transformations. The main advantages of organocatalysts over transition metal catalysts are the fewer toxicity issues associated with their use, the decreased cost and effort required to prepare them and the greater tolerance of the catalysts to air and water. The first organocatalysts were amino acid derived and were used in aldol, Mannich and Diels Alder reactions. Since then a vast selection of catalysts have been developed which operate through various modes of activation.[3]

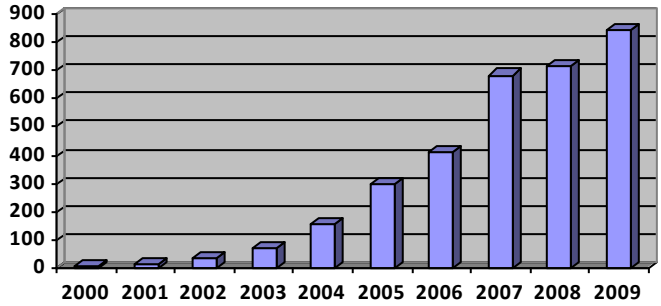
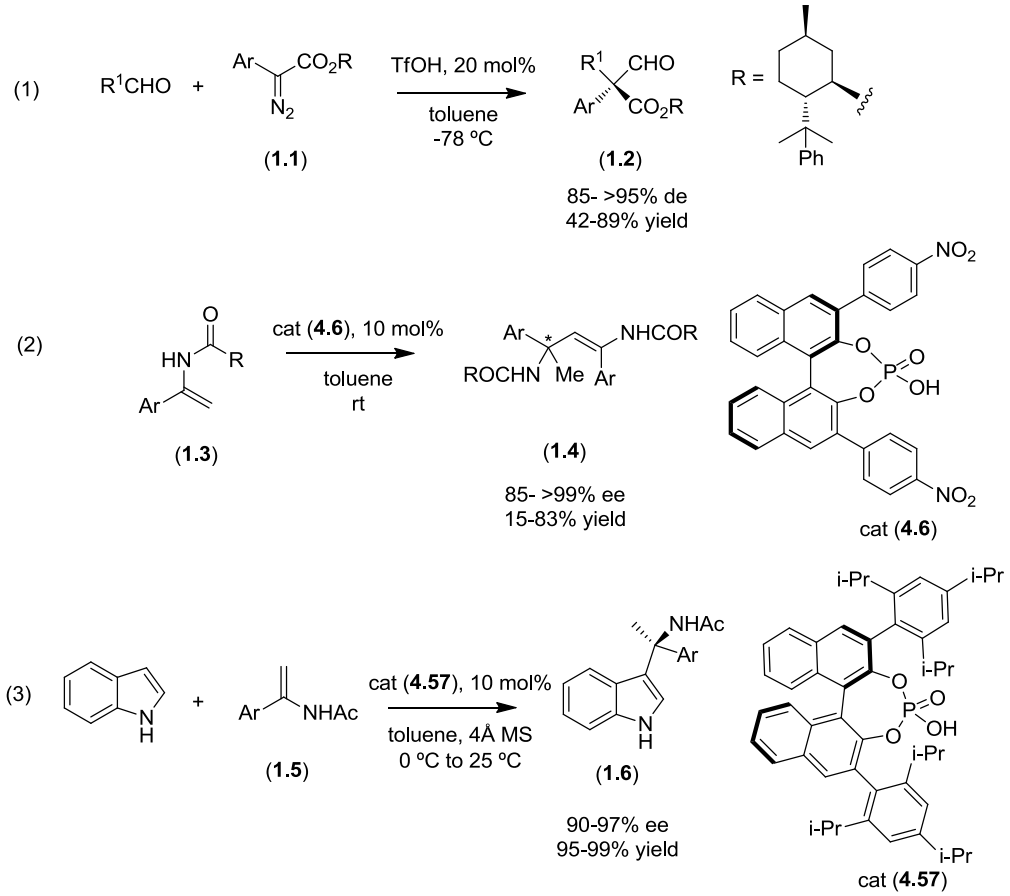


Figure 1.1: SciFinder hits for "Organocatalysis" from 2000 to 2009

1.2 The use of Brønsted acid organocatalysis in chiral quaternary centre formation

The formation of a chiral quaternary centre with high stereocontrol represents a major challenge to chemists. The issues of steric hindrance associated with the creation of a quaternary centre mean that harsh reaction conditions are often required and the scope of nucleophiles and electrophiles employed is limited. The growth in the field of organocatalysis over the last few years has led to the development of numerous methodologies where organocatalysts have been employed to promote the formation of quaternary stereocentres with excellent stereocontrol and under relatively mild reaction conditions. The use of Brønsted acid catalysis in the formation of quaternary centres has been demonstrated recently. Maruoka *et al.* exploited the use of triflic acid as a Brønsted acid catalyst in the stereoselective insertion of (-)-phenylmenthyl aryldiazoacetates to aldehydes[4] (Scheme 1.1 (1)). By using a phenylmenthyl moiety as a chiral auxiliary, products were formed in excellent diastereomeric excesses and in good yields. Later in 2008, Tsogoeva and co-workers published an asymmetric self coupling reaction of enamides in the presence of a BINOL-derived phosphoric acid catalyst.[5] The quaternary stereocentres in the products were formed in excellent enantioselectivity (Scheme 1.1 (2)). Zhou and co-workers also used a BINOL-derived phosphoric acid catalyst in their asymmetric Friedel-Crafts reaction of indole with variously substituted

enamides.[6] The chiral amines possessing a quaternary stereocentre were formed in high enantioselectivity and in high yield (Scheme 1.1 (3)).



Scheme 1.1: Examples of Brønsted acid catalysed quaternary centre formation

1.3 Thesis aims

The use of Brønsted acid catalysis to form chiral quaternary centres has only recently been addressed and only a few examples of this mode of catalysis exist in the literature.[7] The aim of this thesis is to explore the use of chiral and achiral Brønsted acid catalysts in the construction of chiral quaternary centres with high stereocontrol formed from reactive *N*-acyl iminium electrophiles.[8] New powerful methodologies will be developed and applied to the synthesis of a complex natural product bearing a chiral quaternary centre.

Chapter 2: Proline as a chiral template for quaternary centre formation

2.1 Introduction

2.1.1 Introduction to chiral auxiliaries and chiral templates

Chiral auxiliaries are enantiomerically pure compounds which are covalently bonded to a substrate and influence the stereochemical outcome of a reaction by their presence.[9] They are typically small molecules bearing a functional group which will undergo a stoichiometric reaction with a reagent to yield the substrate for the diastereomeric selective reaction. Using steric hindrance or directing groups during the stereoselective reaction, they are able to influence the stereochemical formation of a new chiral centre. Physical separation of diastereomeric products followed by removal of the chiral auxiliary, which can be recycled, results in the formation of products in high enantio- or diastereomeric excess. Chiral templates only differ from chiral auxiliaries in that the chiral templates cannot be recycled and are used up in stoichiometric quantities during an asymmetric reaction.

The extensive accumulated knowledge regarding chiral auxiliaries and chiral templates means their reactivity and stereoselectivity is generally predictable. They provide a reliable means of synthesising enantiomerically enriched compounds which would otherwise not always be readily obtainable, and they have been used widely as a tool in the synthesis of therapeutics.

2.1.2 The use of amino acid derived chiral auxiliaries and chiral templates

2.1.2.1 SAMP as a chiral auxiliary and as a chiral template

(*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP) is a chiral hydrazine auxiliary derived from (*S*)-proline (Figure 2.1). It was first developed by Enders and Eichenauer[10] in 1976 and has been used extensively in many organic reactions such as in alkylation reactions,[11] Michael additions,[12] Diels-Alder reactions[13] and in nucleophilic addition reactions to the hydrazone C=N bond formed on addition of SAMP to a carbonyl.[14,15]

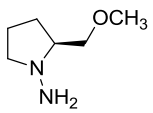
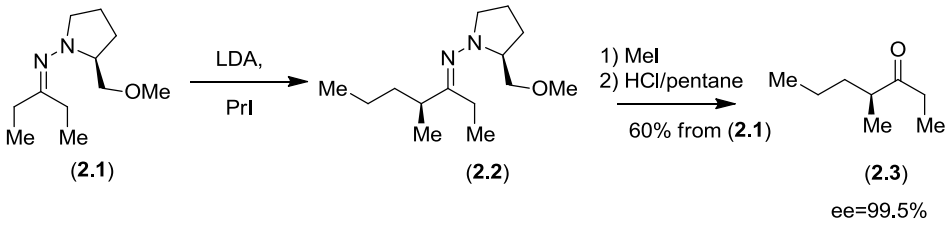


Figure 2.1: SAMP

1) Applications

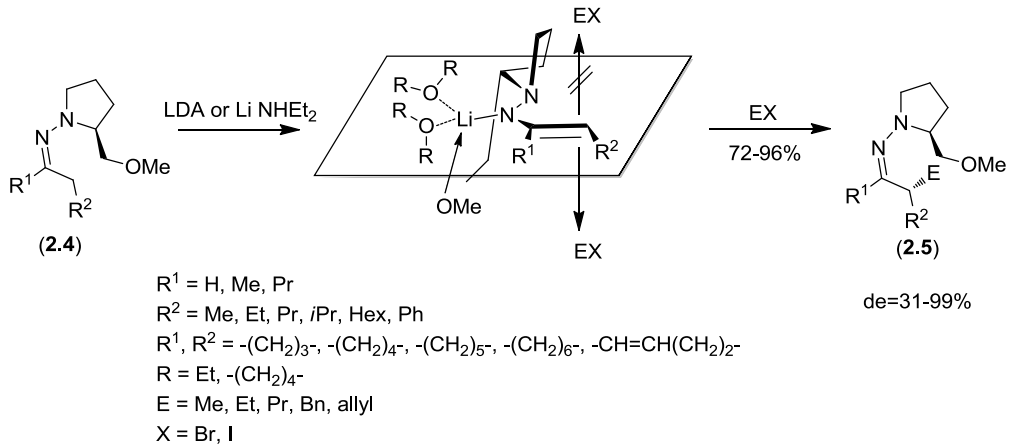
Alkylations:

SAMP is most frequently used as a chiral auxiliary in alkylation reactions. One of the first applications of SAMP was in the synthesis of the alarm pheromone from the ant *Atta texana*.[16] This began with the preparation of hydrazone (**2.1**) by heating SAMP and ethyl ketone to 60 ºC for 20 hours. With the chiral auxiliary in place, the lithium aza enolate was generated using LDA which was able to undergo a diastereoselective nucleophilic substitution reaction with iodopropane to yield hydrazone (**2.2**). Subsequent hydrolytic cleavage of the auxiliary afforded the product (**2.3**) in 99.5% ee with an overall yield of 60% from (**2.1**) (Scheme 2.1).



Scheme 2.1: Preparation of (**2.3**) by diastereoselectively controlled alkylation

To explain the stereochemical preference of the alkylation reaction, a transition state was proposed which featured chelation of the methoxy-group and hydrazine with lithium of the aza enolate to form a six-membered ring (Scheme 2.2). This chelation effect caused the SAMP auxiliary to shield the *Re*-face of the aza enolate and resulted in the preferential attack of the electrophile from the *Si*-face. Evidence for the proposed transition state comes from trapping experiments[17], spectroscopy[18] and X-ray analysis.[19]

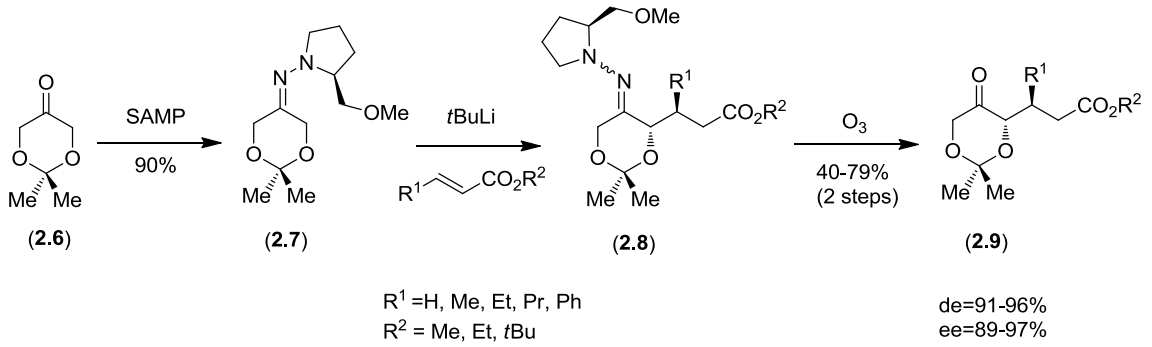


Scheme 2.2: Transition state model proposed for SAMP assisted alkylation reactions

Michael additions:

The use of SAMP as a chiral auxiliary was extended to the formation of chiral Michael addition products starting from a dioxanone derivative (**2.6**). Formation of the aza enolate from hydrazone

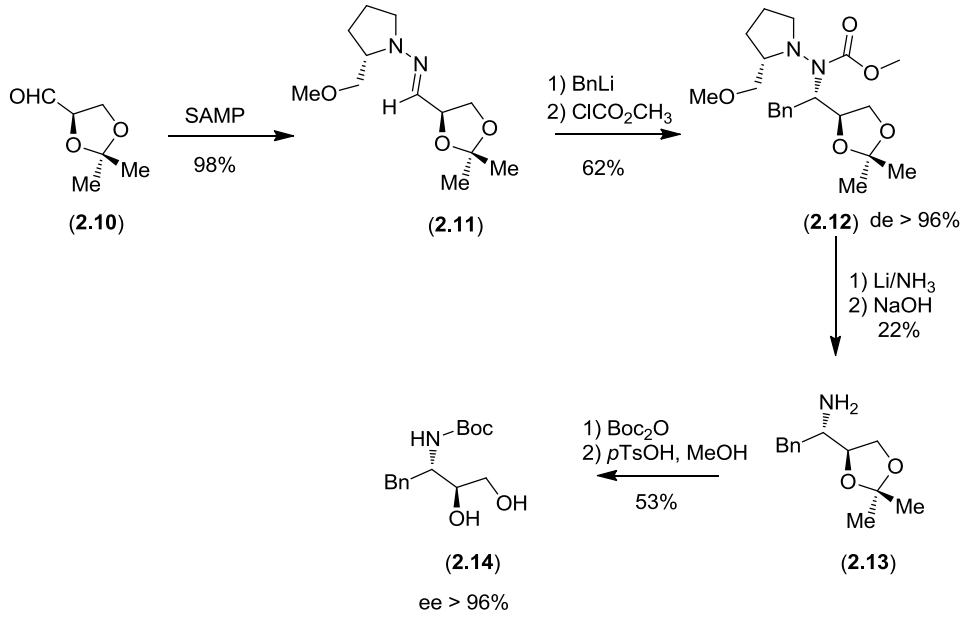
(**2.7**) with ^{t}BuLi and subsequent Michael addition to an (*E*)-α,β-unsaturated ester gave the desired Michael adducts (**2.8**).[20] Ozonolysis of the crude reaction product furnished Michael adducts (**2.9**) in moderate to good yields and in high diastereoselectivities and enantioselectivities (Scheme 2.3).



Scheme 2.3: Diastereoselective Michael addition using SAMP

Addition to the SAMP hydrazone:

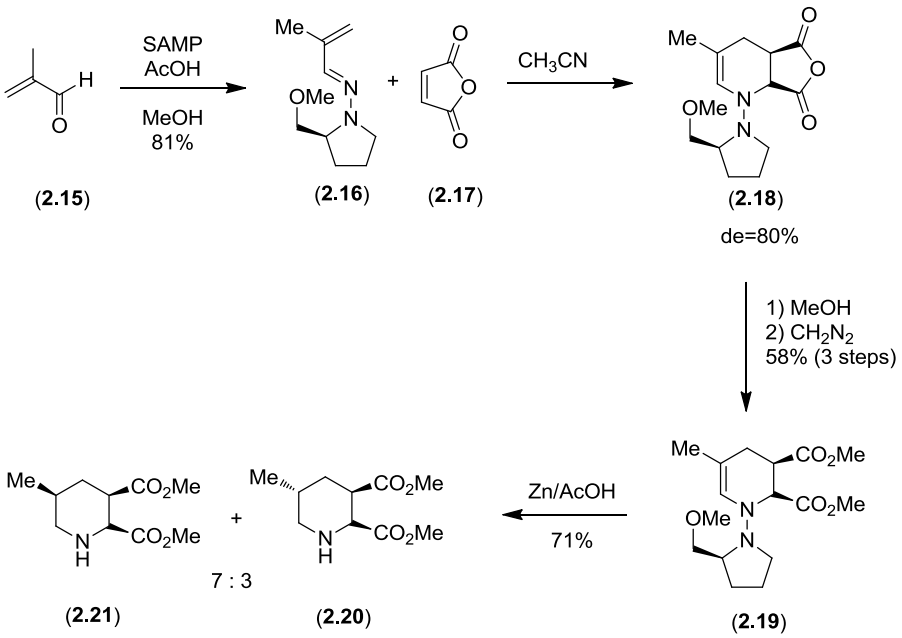
When reacted with an aldehyde SAMP forms a hydrazone which can be attacked by an organometallic reagent via a nucleophilic addition reaction. The organometallic reagents will react with the SAMP hydrazone in a stereoselective fashion to form products in high enantiomeric and diastereomeric excess. The best results are obtained with organolithium, organocerium, organoytterbium and Grignard reagents. This reaction has been applied to the synthesis of D-phenylalaninol derivatives (Scheme 2.4). The synthesis began with the formation of hydrazone (**2.11**) from the addition of SAMP to protected D-glyceric aldehyde. Benzyl lithium addition was followed by carbamate formation, giving adduct (**2.12**) in 62% yield and in excellent de. Cleavage of the hydrazine bond with lithium and ammonia, and hydrolysis of the carbamate with NaOH afforded amine (**2.13**), which was converted to Boc protected D -phenylalaninol (**2.14**).[21]



Scheme 2.4: The stereoselective addition of benzyl lithium to the SAMP hydrazone

Hetero-Diels-Alder reactions:

The use of SAMP in hetero-Diels-Alder reactions is illustrated below in the preparation of piperidine derivatives (**2.20**) and (**2.21**)[22] (Scheme 2.5).

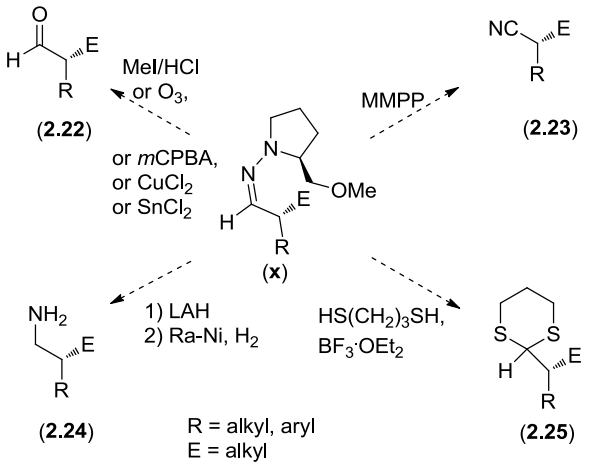


Scheme 2.5: The use of SAMP in hetero-Diels-Alder reactions

Formation of hetero-Diels-Alder adduct (**2.18**) in a high diastereomeric excess was achieved by reaction of dienophile (**2.17**) with diene (**2.16**) at room temperature in acetonitrile. Ring opening of the anhydride with methanol and esterification yielded adduct (**2.19**) which, after cleavage of the N-N bond with zinc and acetic acid gave the corresponding piperidine derivatives without epimerisation or racemisation of the preformed stereocentres. The double bond was reduced unselectively in the auxiliary cleavage reaction and gave epimers (**2.21**) and (**2.20**) in a 7 : 3 ratio respectively.

2) Cleavage

The SAMP auxiliary can be removed by various methods such as oxidative cleavage with ozone or *m*CPBA; hydrolytic cleavage with $CuCl_2$ or MeI/HCl; and reductive cleavage with $SnCl_2$. Besides regenerating the parent aldehyde by auxiliary cleavage, new functionalities such as dithian (**2.25**),[23] nitrile (**2.23**)[24], and amino groups (**2.24**)[25] can be incorporated (Scheme 2.6).



Scheme 2.6: Methods of auxiliary cleavage and incorporation of new functionality

Since the mid 1970's, SAMP has been used as the chiral auxiliary and chiral template of choice in many carbon-carbon bond forming reactions to generate enantiomeric and diastereomeric products. The success of SAMP as a chiral auxiliary and chiral template has promoted the development of other amino acid derived chiral auxiliaries.

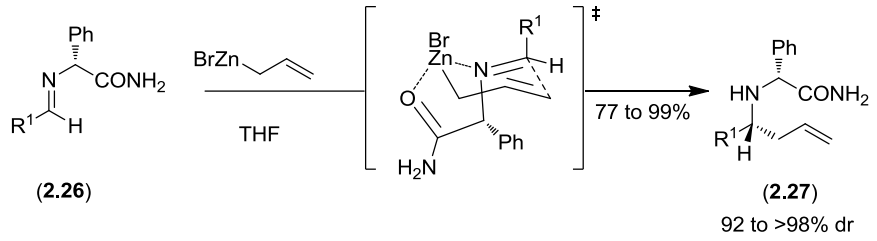
2.1.2.2 (*R*)-Phenylglycine amide as a chiral template

(*R*)-Phenylglycine amide became readily accessible when used as an important intermediate in the enzymatic synthesis of β-lactam antibodies on an industrial scale.[26] It is possible to resolve (*R*)-phenylglycine amide from racemic phenylglycine amide by hydrolysis catalysed by aminopeptidase or by using (*S*)-mandelic acid as a resolving agent.[27]

1) Application

Nucleophilic addition reactions:

(*R*)-Phenylglycine amide has been used as a chiral template to promote the diastereoselective addition of allylzinc bromide to imines by Kellogg and co-workers[28] (Scheme 2.7). The resulting homoallylamines (**2.27**) were formed in good yield and in excellent diastereoselectivity and allyl zinc bromide proved to be an excellent choice of nucleophile even in the presence of a phenolic hydroxyl group. A transition state was proposed to rationalise the observed stereochemical outcome. This featured the chelation of zinc by the two heteroatoms in the phenylglycine moiety and the arrangement of the allyl chain in a six-membered Zimmerman Traxler[29] like transition state with the imine.

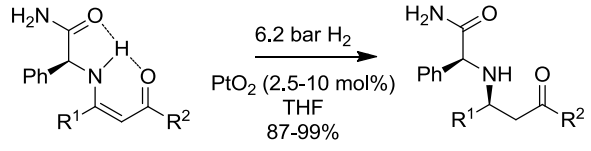


R^1 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-PhC_6H_4, *p*-NO_2CH_4, 3-piperonyl, *p*-HOC_6H_4, 2,5-$(MeO)_2C_6H_4$, 3-pyridyl, 2-furyl, 2-thiophene, *t*-Bu, *i*-Pr, *i*-Bu

Scheme 2.7: (*R*)-Phenylglycine amide as a chiral template in addition of zinc bromide to imines

Hydrogenation reactions:

In 2003 Ikemoto, Tellers, and Rivera reported an asymmetric hydrogenation reaction of an enamine, employing (*S*)-phenylglycine amide as a chiral template.[30] The high diastereoselectivities observed were thought to result from a hydrogen bonding interaction between the secondary amine proton and the sp^2 oxygen atoms. This arrangement resulted in a planar structure with the phenyl group of the glycine template shielding one of the diastereotopic faces. As shown below, the phenyl moiety occupies the *Re*-face of enamine (**2.28**) and as consequence diastereoselective hydrogenation will occur from the *Si*-face to yield products (**2.29**) (Scheme 2.8).

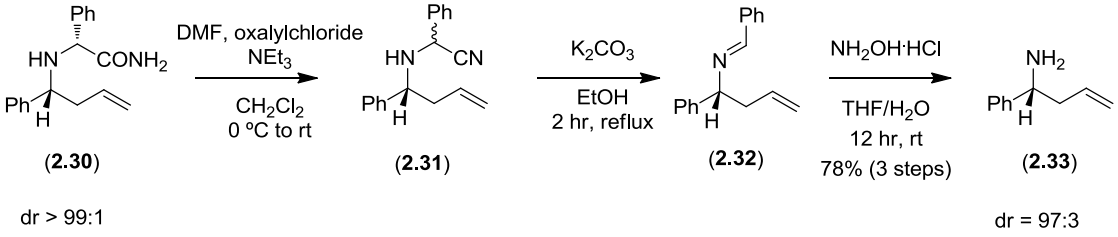


R^1 = Me, *i*-Pr, Bn, *p*-$CH_3OC_6H_4$, *p*-$CF_3C_6H_4$
R^2 = OMe, NH_2, *N*-piperidyl

Scheme 2.8: Diastereoselective hydrogenation employing (*S*)-phenylglycine amide as a chiral template

2) Cleavage

The removal of the phenylglycine amide moiety has been achieved using hydrogenation although unsurprisingly this has only been successful in the absence of functional groups which are sensitive to hydrogenation. For example, in the work described above by Kellog *et al*. (Scheme 2.7) the removal of the (*R*)-phenylglycine amide chiral template of homoallylamines (**2.27**) by hydrogenation resulted in the loss of the allylic functionality. In order to address this problem, a new approach to the cleavage of phenylglycine amide was developed by Kellog and co-workers which avoided hydrogenolysis[28] (Scheme 2.9).



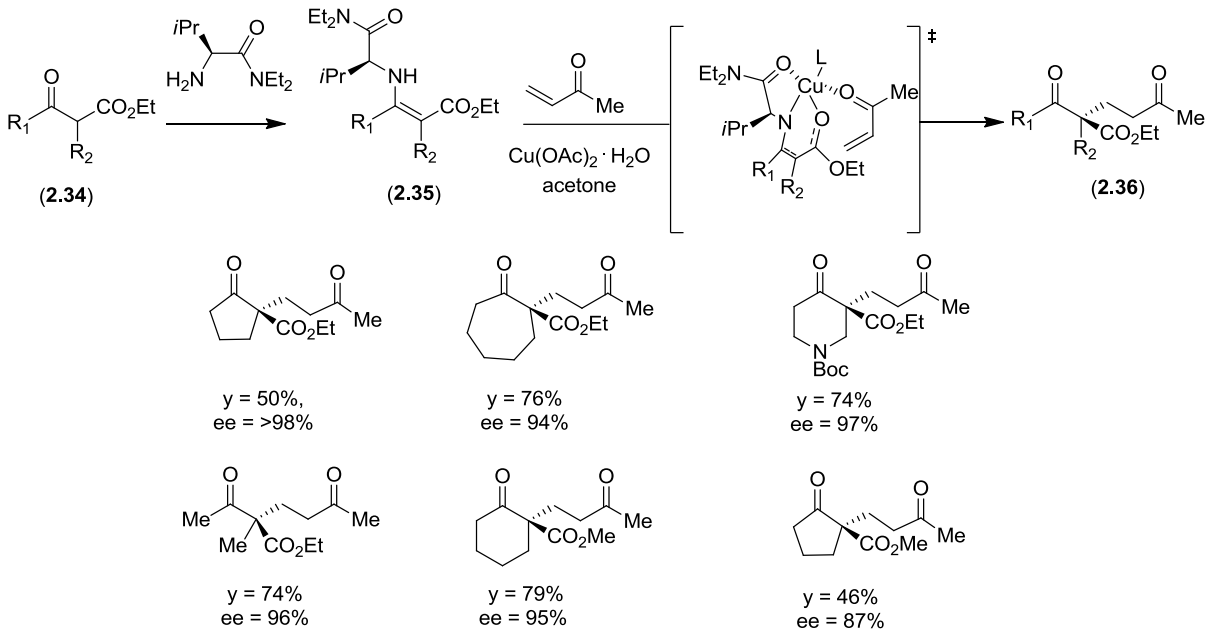
Scheme 2.9: Removal of (*R*)-phenylglycine amide

The removal of (*R*)-phenylglycine amide began with the dehydration of the amide using DMF and oxalylchloride to furnish the nitrile (**2.31**). This was followed by treatment with potassium carbonate. The benzilidine group was removed on treatment with hydroxylamine hydrochloride to yield amine (**2.33**) in 78% overall yield from (**2.30**).

2.1.3 Formation of quaternary centres using amino acid derived chiral auxiliaries and chiral templates

2.1.3.1 L-valine as a chiral auxiliary in an enantioselective Michael addition reaction

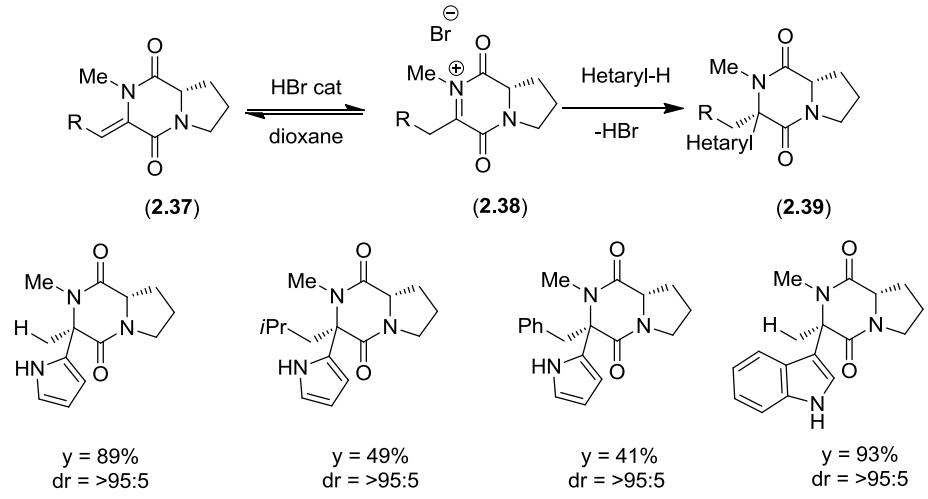
Christoffers and Mann developed a highly enantioselective copper catalysed Michael addition to access 1,3-dicarbonyls bearing a quaternary centre by employing L-valine diethylamide as a chiral auxiliary[31] (Scheme 2.10). Under mild reaction conditions, a quaternary centre α to the carbonyl was formed in high enantiomeric excess and a series of 1,3-dicarbonyl derivatives (**2.36**) were afforded. The reaction sequence began with the formation of enamine (**2.35**), which under Cu (II) catalysis underwent a Michael addition reaction to methyl vinyl ketone to give Michael adducts (**2.36**). The L-valine chiral auxiliary was hydrolytically cleaved in the reaction conditions and was isolated almost quantitatively from the reaction mixture on extraction. A transition state model was proposed in order to rationalise the stereochemical outcome of the reaction. Enamine (**2.35**) was thought to act as a tridentate ligand and chelate to the Cu (II) species to form a planar Michael donor with the isopropyl group of the auxiliary shielding the *Re*-face. The blocking of the *Re*-face by the isopropyl group resulted in the Michael acceptor coordinating and being activated from the *Si*-face of the complex to give the (*R*)-configuration in the product (Scheme 2.10).



Scheme 2.10: L-valine as the chiral auxiliary in enantioselective Michael addition

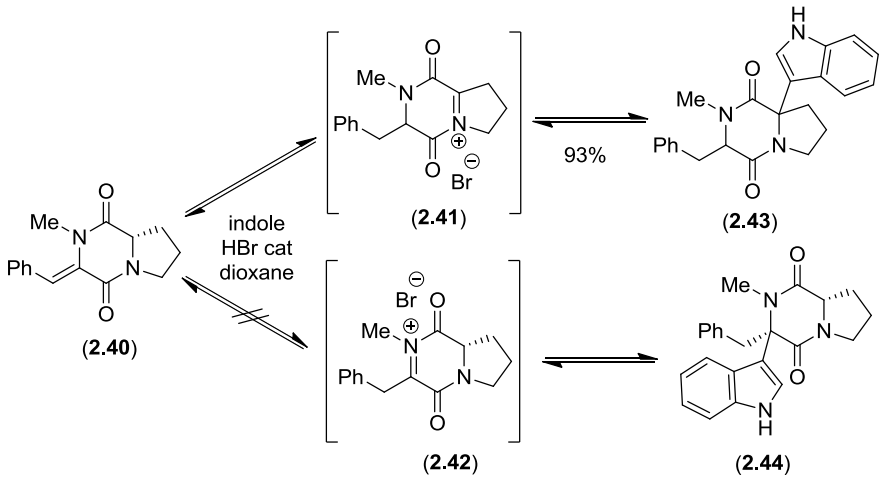
2.1.3.2 Proline derived diketopiperazines (DKPs) as chiral templates in quaternary centre formation

Liebscher *et al.*[32] developed a method for the addition of *N*-heteroaromatics to 3-alkylidine or 3-benzylidine-2,4-diketopiperazines in the presence of a catalytic amount of HBr to access 3-alkyl-2,5-diketopiperazines in high diastereomeric ratios as precursors to quaternary α-amino acids. 3-alkylidine-2,4-diketopiperazines were readily accessed from proline and were used as chiral templates (Scheme 2.11). Under HBr catalysis DKP (**2.37**) formed an iminium ion (**2.38**) which could undergo a Mannich type reaction with pyrrole or indole to create a new quaternary centre in high diastereoselectivity. Attack of the *N*-heteroaromatic occurred from the less hindered convex side of the fused ring system.



Scheme 2.11: Acid catalysed addition of *N*-heteroaromatics to diketopiperazines

This methodology led to the formation of products with differently substituted quaternary centres in good yields and in high diastereomeric ratios (Scheme 2.11). When indole was employed in the addition to DKPs bearing bulky R substituents such as phenyl, a constitutional isomeric product was formed (**2.43**)[33] (Scheme 2.12). Under acidic conditions the C-C double bond was able to migrate via a series of protonation and deprotonation steps. The equilibrium was found to lie towards the product which offered the greatest degree of conformational flexibility to the substituents attached to the *N*-atoms and adjacent *C*-atoms. Compound (**2.43**) was afforded in 93% yield and was thought to have been formed via iminium ion (**2.41**).



Scheme 2.12: Acid catalysed isomerisation of double bonds leading to one of two regioisomers

Further investigation of the C-C double bond migration showed that in the absence of steric interactions, i.e. when *N*-unsubstituted DKPs were used, no migration of the double bond occurred, only *E/Z* isomerisation.

2.2 Concept and Aims

Liebscher *et al.* have developed an approach to access quaternary centres using a diketopiperazine derived from proline. They demonstrated that both pyrrole and indole can be used as nucleophiles in the Mannich type addition reaction to give quaternary centres in high diastereomeric ratios. However, they did not explore the use of 3-substituted indoles in order to probe the methodology further, and give rise to compounds which could be used as intermediates in natural product synthesis.

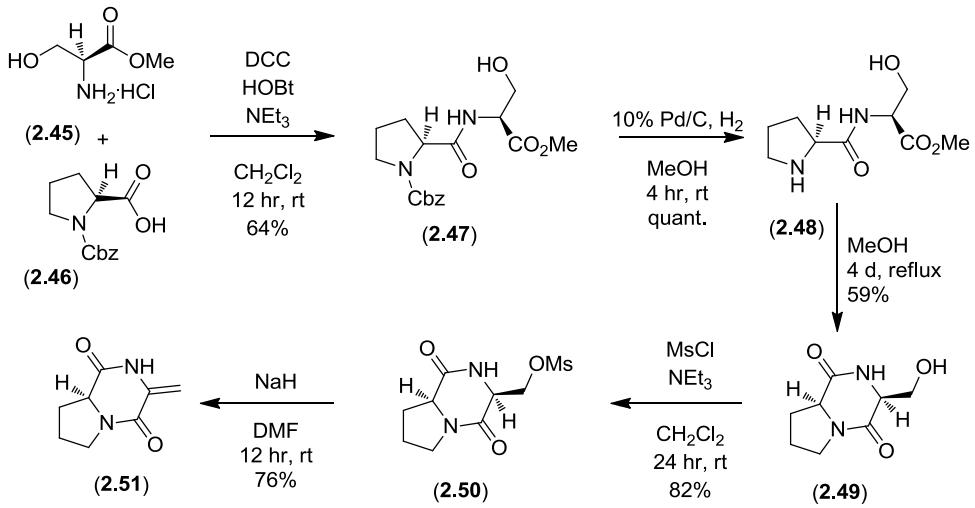
Specifically, the aims of this study were:

1) To develop and optimise the synthesis of an *N*-unsubstituted DKP.
2) To explore the reactions of DKPs with various 3-substituted indole nucleophiles.
3) To identify a natural product with the same quaternary centre motif and apply the methodology to its synthesis.

2.3 Results and Discussion

2.3.1 Initial construction of the diketopiperazine (DKP) chiral building block

α,β-Unsaturated amide (**2.51**) could be synthesised from diketopiperazine (**2.49**), which had been previously synthesised by Falorni *et al*.[34] The synthesis began with the amide coupling of L-serine methyl ester hydrochloride (**2.45**) with Cbz-protected L-proline (**2.46**), followed by hydrogenation of the Cbz group to afford dipeptide (**2.48**) and subsequent heat induced cyclisation to yield (**2.49**) (Scheme 2.13).



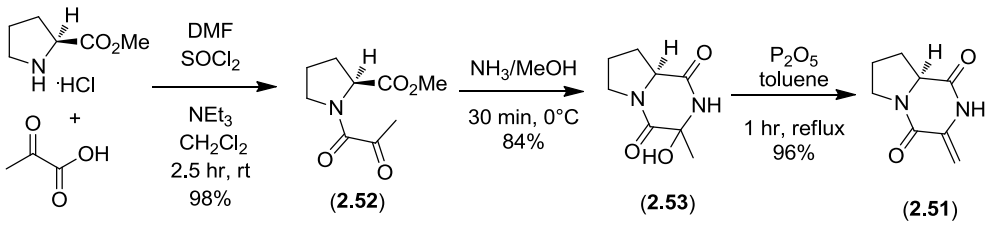
Scheme 2.13: Synthesis of α,β-unsaturated amide (**2.51**)

Falorni *et al* used 4-methyl morpholine and ethylchloroformate to facilitate the amide coupling, but when these conditions were tried only a 20% yield was obtained. More conventional coupling conditions using DCC, HOBt and NEt_3 in dichloromethane were investigated and resulted in an improved yield of 64%. Dipeptide (**2.47**) was deprotected to give adduct (**2.48**) using typical hydrogenation conditions with no need for further purification before being refluxed in MeOH in order to effect cyclisation. Falorni *et al.* obtained diketopiperazine (**2.49**) in poor 36% yield, probably due to the concentrated conditions (1.6 M) in which they conducted the intramolecular cyclisation of dipeptide (**2.48**) as this could have promoted intermolecular side reactions. Using a reduced concentration of 0.05 M diketopiperazine (**2.49**) was afforded in a respectable 59% yield, although the reaction required an extra two days to reach completion.

Having successfully synthesised diketopiperazine (**2.49**), the formation of α,β-unsaturated amide (**2.51**) was achieved by mesylation of the primary alcohol followed by elimination with NaH in DMF. This was confirmed by the presence of the two methylene protons as singlets in the ^{1}H NMR spectrum at δ 4.82 and δ 5.53 ppm.

2.3.2 Improved synthesis of the DKP

Due to the lengthy and relatively poor yielding synthesis of α,β-unsaturated amide (**2.51**) via DKP (**2.49**), an alternative route that did not involve the loss of a chiral centre was investigated, and a more efficient synthesis via formation of tertiary alcohol (**2.53**) was found (Scheme 2.14). This synthesis of tertiary alcohol (**2.53**) had been employed by Bycroft and Lee in 1975 in their synthesis of α-amino acids from α-keto acids[35] and was subsequently used by Sanz-Cervera *et al*.[36] however, experimental procedures were absent from both publications.



Scheme 2.14: Synthesis of α,β-unsaturated amide (**2.51**) via tertiary alcohol (**2.53**)

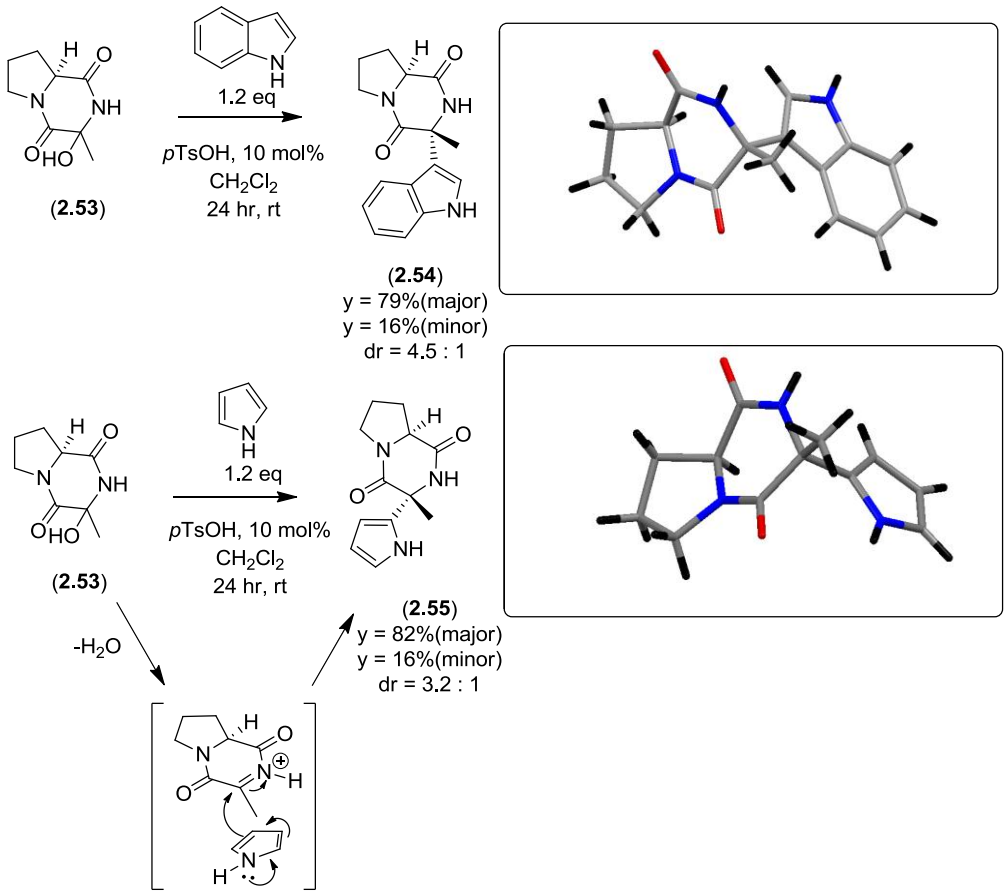
The first step was the coupling of pyruvic acid with commercially available L-proline methyl ester hydrochloride to give amide (**2.52**). Standard coupling conditions using DCC, HOBt and NEt_3 in dichloromethane afforded (**2.52**) in poor yield (13%), after purification by column chromatography, despite the 70-80% yields reported. A procedure[37] was found for the generation of pyruvyl chloride *in situ*, prior to the addition of L-proline methyl ester hydrochloride, this resulted in an impressive yield, 98% of adduct (**2.52**) which did not require further purification. Compound (**2.52**) was found to exist as a pair of rotamers which after reaction with anhydrous ammonia in methanol spontaneously cyclised to afford tertiary alcohol (**2.53**) in 84 % yield (Scheme 2.14).

Bycroft and Lee dehydrated the tertiary alcohol of (**2.53**) with trifluoroacetic acid[35] but no procedure or yield was available to follow; stirring tertiary alcohol (**2.53**) in neat TFA for three days at room temperature gave 43% of a product which could not be satisfactorily purified. However on optimisation it was found that the use of phosphorous pentoxide in refluxing toluene with a Dean-Stark apparatus, furnished adduct (**2.51**) in an impressive 96% yield.

2.3.3 Nucleophilic additions to iminium ions generated *in situ*

After having successfully optimised a route to α,β-unsaturated amide (**2.51**), it was proposed that instead of dehydrating tertiary alcohol (**2.53**) prior to the reaction, it could be dehydrated *in situ* using catalytic acid and thus generate an iminium ion. This would be able to undergo a nucleophilic addition reaction with an *N*-heteroaromatic nucleophile to generate a chiral quaternary centre and furnish the product. This proposal proved successful, and when tertiary alcohol (**2.53**) was subjected to catalytic *p*-toluenesulphonic acid in dichloromethane at room temperature in the presence of indole or pyrrole, a diastereoselective nucleophilic addition reaction occurred. Single regioisomers of indole addition product (**2.54**) and pyrrole addition product (**2.55**) were obtained in

95% and 98% yields respectively and in diastereomeric ratios of 4.5 : 1 and 3.2 : 1 respectively. These diastereomeric ratios are significantly lower than those obtained by Liebscher *et al.*[32] where an *N*-alkylated DKP was employed in the reaction. *N*-alkylation of the DKP obviously results in enhanced diastereoselectivity. Single crystal X-ray crystallography of the major diastereomers of both products proved the relative stereochemistry. The absolute stereochemistry could be assigned from the fixed stereocentre of L-proline and showed that the addition of indole and pyrrole to DKP (**2.53**) had occurred from the *Re* convex face (Scheme 2.15).

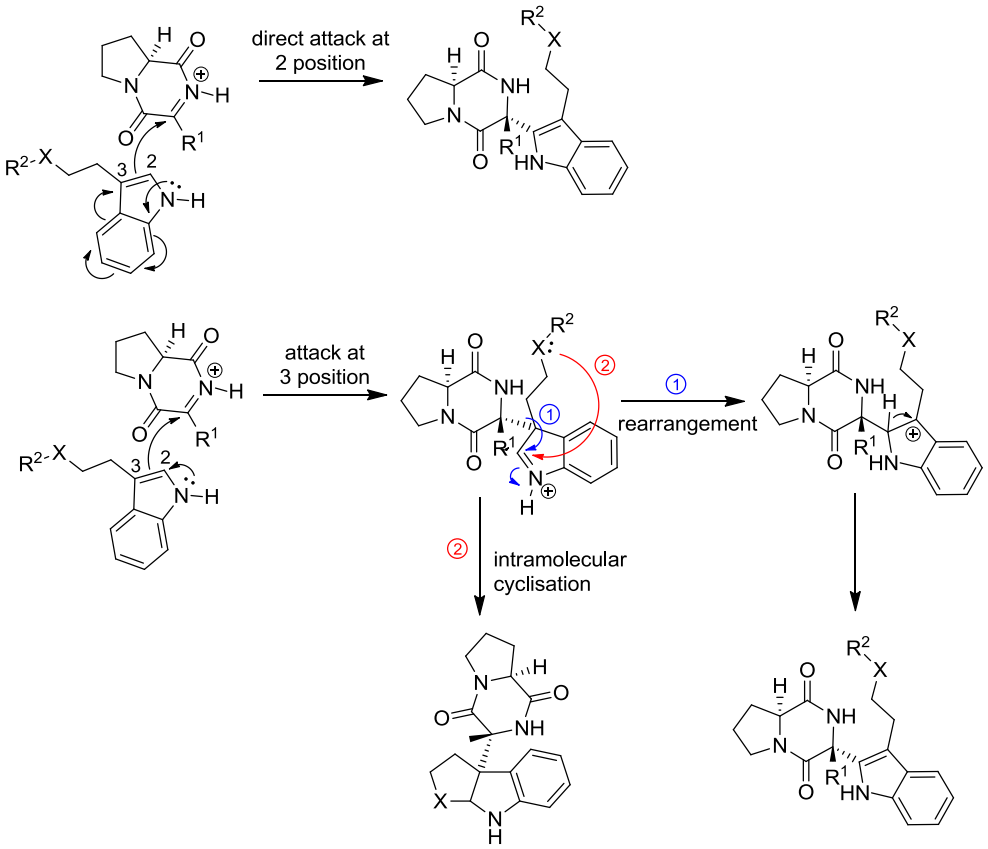


Scheme 2.15: Diastereoselective addition reactions of *N*-heteroaromatics to DKP (**2.53**) and x-ray crystal structures showing the relative stereochemistry of the major diastereomers for the corresponding products

2.3.4 The use of 3-substituted indoles as nucleophiles

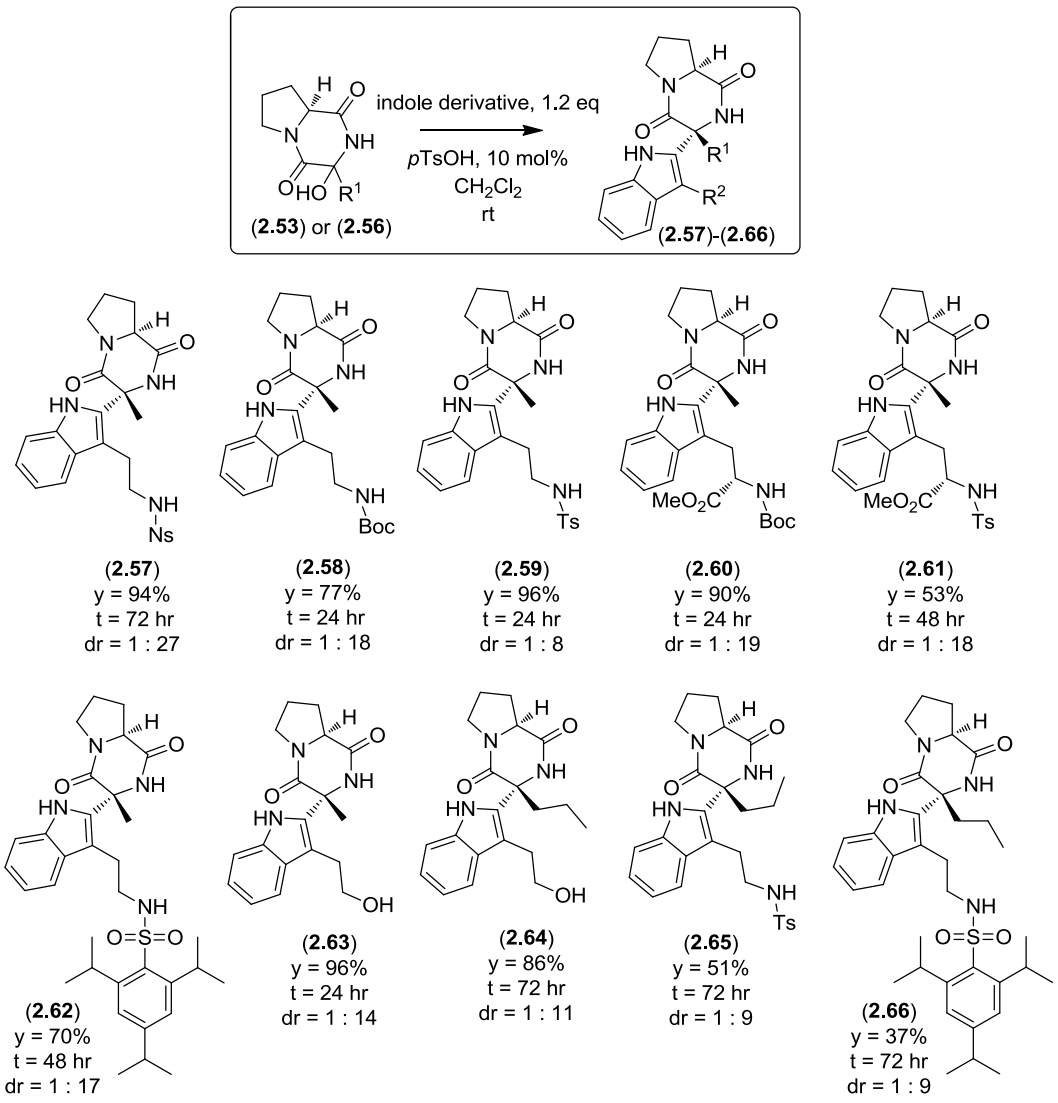
After obtaining pleasing results from the use of tertiary alcohol (**2.53**) to generate iminium ions *in situ*, attention was turned to the extension of the methodology by employing 3-substituted indoles. Addition reactions of 3-substitued indoles to Michael acceptor 2-cyclohexenone was reported in 2005 by McClusky *et al.*[38] The 3-substituted indoles were found not only to react at the 2-position of indole, but also on the indole nitrogen atom to form *N*-alkylated indoles under Bi (III) Lewis acidic conditions. Using the conditions established for the addition of pyrrole and indole to DKP (**2.53**), a range of 3-substituted indoles were screened. Fortunately none of the undesired *N*-alkylated products were observed and only C-2 addition had occurred. The mechanism by which the addition reaction took place was unknown but it seemed likely that direct attack from the 2-position

of indole occurred rather than attack from the 3-position and subsequent rearrangement, due to steric hindrance at the 3-position (Scheme 2.16).



Scheme 2.16: Proposed reaction pathways to explain observed products

Had attack occurred from the 3-position, then intramolecular cyclisation of the tryptamine derivative onto the 2-position of indole could have afforded cyclised products.[39,40] However, these were not observed in the crude ^{1}H NMR. Instead, chiral quaternary centres were formed to give a range of compounds possessing different side chains at the C-3 indole position in good to high diastereomeric ratios and in good yield (Scheme 2.17). Tryptamine derivatives, (**2.57**), (**2.58**), (**2.59**) and (**2.62**), and tryptophan derivatives (**2.60**) and (**2.61**) were obtained in high yields and tryptophol addition to tertiary alcohol (**2.53**) furnished product (**2.63**) in an excellent 96% yield. Tertiary alcohol (**2.56**) was developed with a propyl chain at R^1, and was also found to undergo addition reactions with 3-substituted indoles. The products (**2.64**), (**2.65**) and (**2.66**) were obtained in lower yield and required longer reaction times than the corresponding adducts where R^1 was a methyl group. This was probably due to the increased steric hindrance caused by the propyl chain in the formation of the quaternary centre by nucleophilic addition to the iminium ion.



Scheme 2.17: Methodology scope

The relative stereochemistry of (**2.62**) was confirmed by single crystal x-ray diffraction and the absolute stereochemistry was assigned from the fixed stereocentre of L-proline. This assignment was consistent with attack from the *Re*, convex face of DKP (**2.53**) (Figure 2.2).

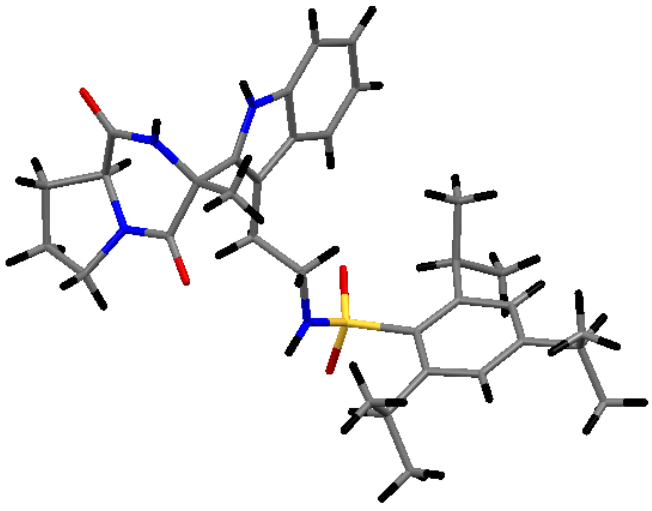
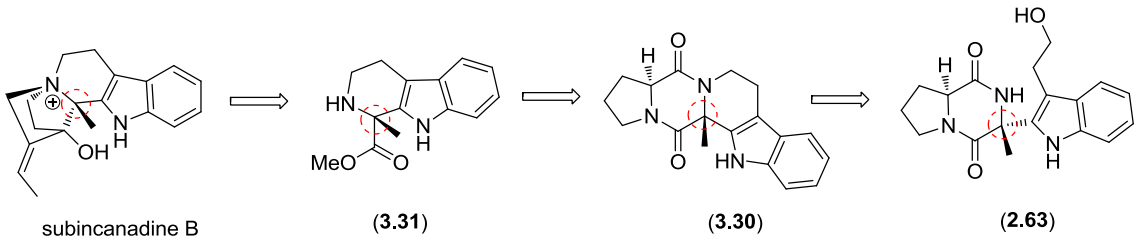


Figure 2.2: X-ray crystal structure of (**2.62**)

2.3.5 The identification of a natural product featuring the quaternary centre motif

With the methodology in place, attention was turned to its application in the synthesis of natural products featuring a quaternary centre adjacent to an amide and an indole moiety. The natural product subincanadine B[41] was found to contain the exact motif constructed in the methodology and could be envisaged as being accessed from tryptophol derivative (**2.63**) (Scheme 2.18).



Scheme 2.18: The quaternary centre motif present in subincanadine B

2.4 Summary

A new methodology resulting in the formation of a chiral quaternary centre by the addition of 3-substituted indoles to L-proline derived DKPs was developed. Products were afforded in excellent yield and in high regio- and diastereoselectivity. The quaternary stereocentre motif was found to resemble the quaternary centre found in the natural product subincanadine B. The application of this methodology to the synthesis of subincanadine B will be reported in the following chapter.

Chapter 3: Synthetic studies towards Subincanadine B – Chiral template approach

3.1 Introduction

3.1.1 Isolation and structural assignment of subincanadine B

Subincanadine B, an indole alkaloid, was first isolated from the Brazilian medicinal plant *Aspidosperma subincanum* in 2002 by Kobayashi *et al.*[41] together with subincanadine A and subincanadines C-F. Subincanadines A-C feature a 1-azoniatricyclo[4.3.3.$0^{1,5}$]-undecane moiety and differ from each other by the stereochemistry at C-17 and by the R group adjacent to the quaternary centre (Figure 3.1).

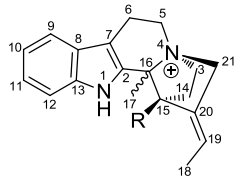


Figure 3.1: Subincanadines A-C

In order to structurally assign the subincanadines a number of spectroscopic techniques were used. A mass spectrum showed a molecular peak at *m/z* 295 corresponding to subincanadine B. The same peak was also seen for subincanadine A. NOE correlation experiments were conducted and showed that in subincanadine B the methyl group at C-16 had an α-orientation, proving that subincanadine B was the C-16 epimer of subincanadine A. The *Z*-configuration of the double bond was assigned from the NOE correlation between H-19 and H_A-21.

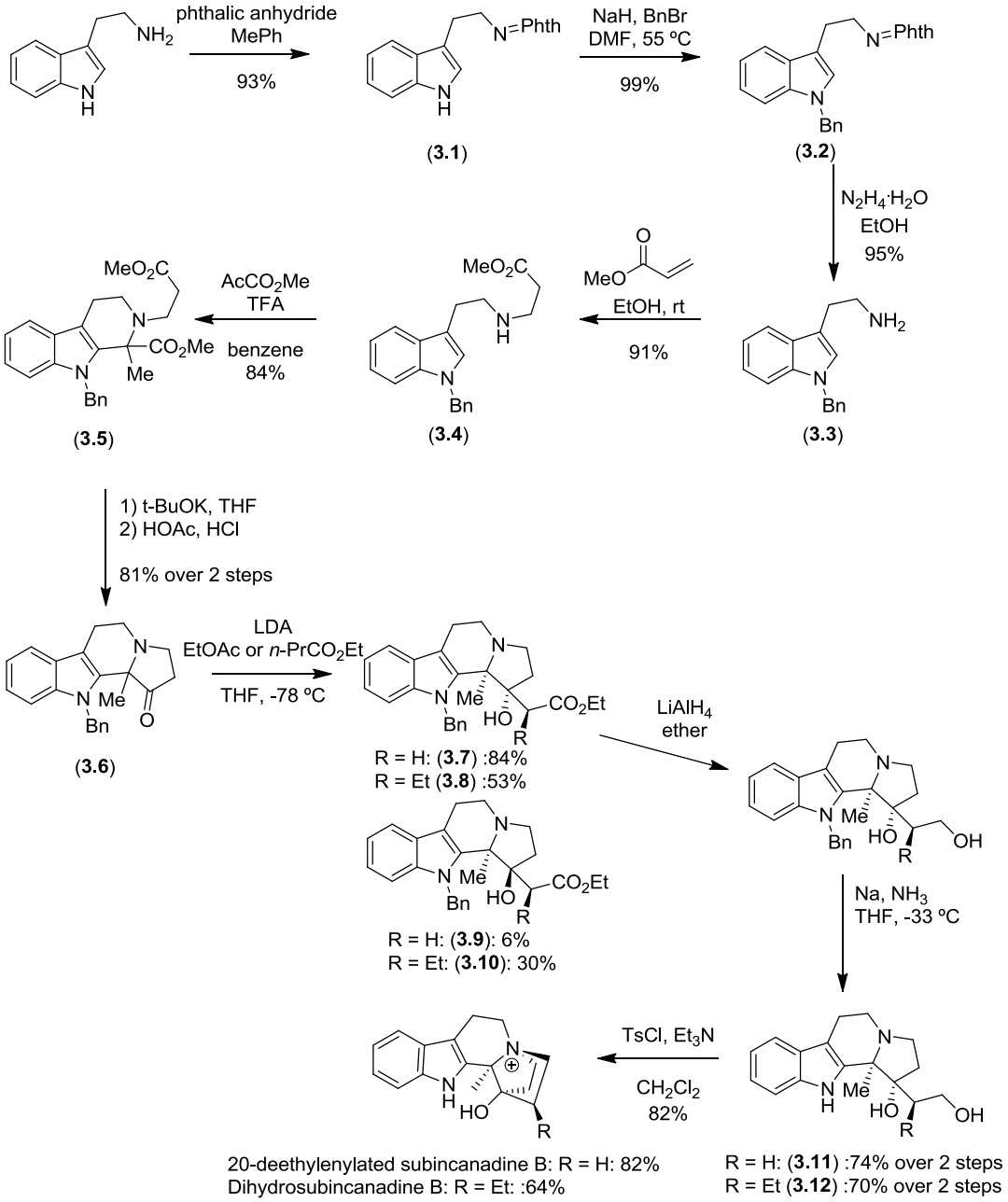
3.1.2 Biological activity of subincanadine B

Although subincanadines E and F were shown to exhibit cytotoxic activity towards murine lymphoma L1210 cells (IC_{50} 0.3 µg/ml and 2.4 µg/ml respectively) and towards human epidermoid carcinoma KB cells (IC_{50} 4.4 µg/ml and 4.8 µg/ml respectively) *in vitro*, subincanadines A-D failed to display any cytotoxic activity.

3.1.3 Previous syntheses of subincanadine B

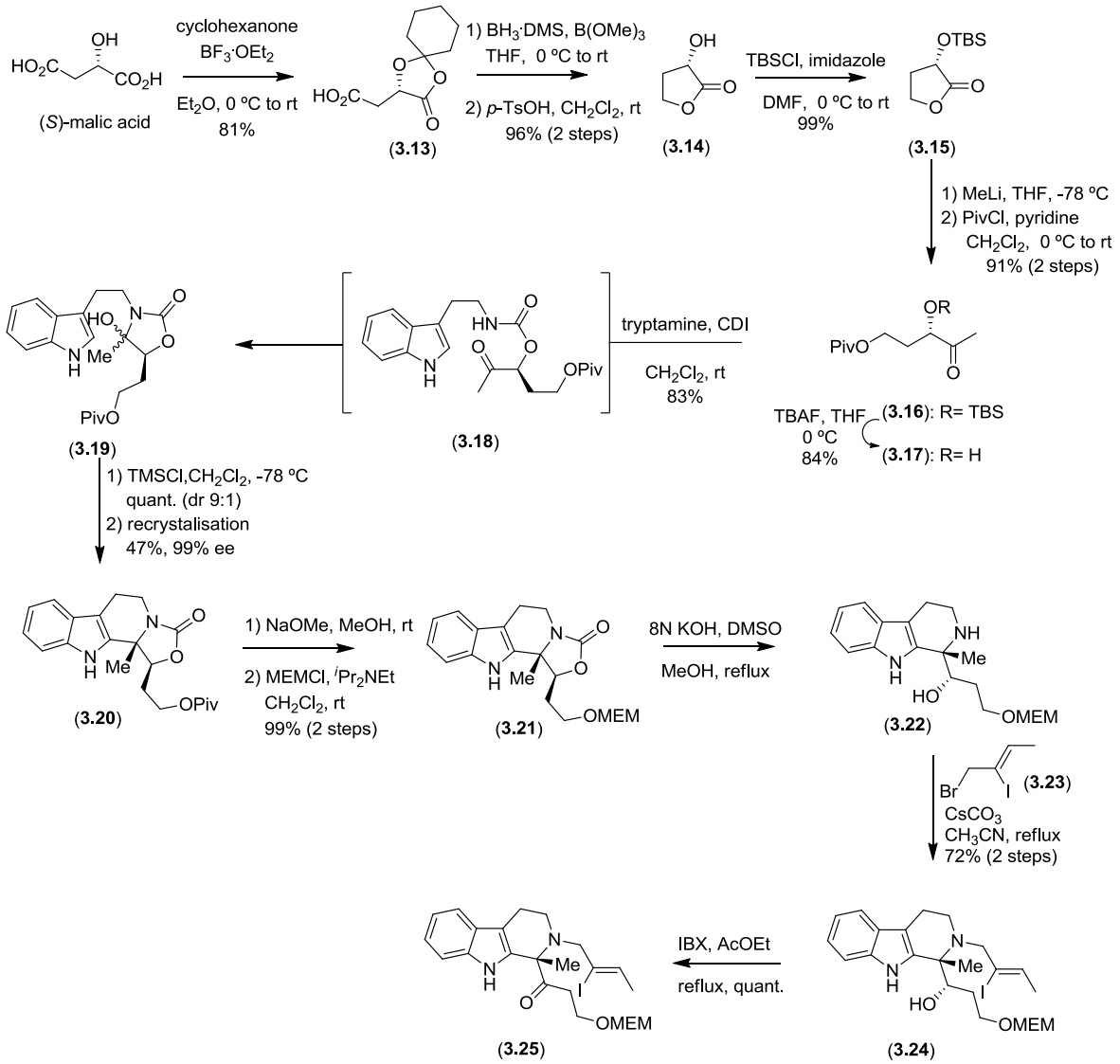
The synthesis of subincanadine B was first attempted by Zhai *et al.*[42] in 2006 where two analogues of the target were made in eleven steps (Scheme 3.1). The key steps in the synthesis were a Pictet-Spengler cyclisation followed by a Dieckmann condensation. The synthesis began with the protection of the primary amine of tryptamine as a phthalamide derivative followed by the benzylation[43] of the indole nitrogen and subsequent transamidation to yield protected tryptamine (**3.3**). Michael addition of tryptamine (**3.3**) with methyl acrylate gave the precursor to the Pictet-Spengler product. In order to affect Pictet-Spengler cyclisation of (**3.4**) it was necessary to use TFA in benzene at reflux for two days. Having obtained the Pictet-Spengler product in 84% yield, the second key step – a Dieckmann condensation, was successfully achieved by reaction of (**3.5**) with potassium *tert*-butoxide followed by decarboxylative hydrolysis with acetic acid and hydrochloric acid. This yielded tetracyclic ketone (**3.6**) as a key intermediate in the synthesis in 81% yield over two steps. With *N*-protected tetracyclic ketone (**3.6**) in hand, their attention was turned to the construction of the azoniacycle of subincanadine B. Many attempts to attach a side chain onto ring D were tried but ketone (**3.6**) proved to be too sterically hindered to allow addition. Thus attention was turned to producing analogues of subincanadine B by employing nucleophiles with less steric bulk, able to undergo nucleophilic addition to ketone (**3.6**). Lithium enolates of ethyl acetate and ethyl butyrate were used to obtain aldol products (**3.7**) and (**3.9**), and (**3.8**) and (**3.10**) respectively as mixtures of separable diastereomers in the ratios 14:1 and 1.73:1 respectively. The relative stereochemistry of the diastereomers was assigned by NOE analysis and the stereoselectivity of nucleophilic addition was explained by nucleophilic addition to the less hindered face of the ketone, i.e. from the opposite face to that occupied by the methyl group at the quaternary centre. Complete reduction of esters (**3.7**) and (**3.8**) with $LiAlH_4$ gave the corresponding diols which were subsequently debenzylated to form *N*-deprotected diols (**3.11**) and (**3.12**) in 74% and 70% respectively over two steps. Spontaneous intramolecular S_N2 reactions took place after tosylation of primary alcohols (**3.11**) and (**3.12**) to form subincanadine B analogues: 20-deethylenylated subincanadine B and dihydrosubincanadine B respectively (Scheme 3.1).

Although Zhai *et al.* had failed to synthesise subincanadine B, they had developed a method for constructing the pentacyclic framework of subincanadine B and outlined the difficulty of successful nucleophilic addition to ketone (**3.6**).



Scheme 3.1: The total synthesis of 20-deethylenylated subincanadine B and dihydrosubincanadine B

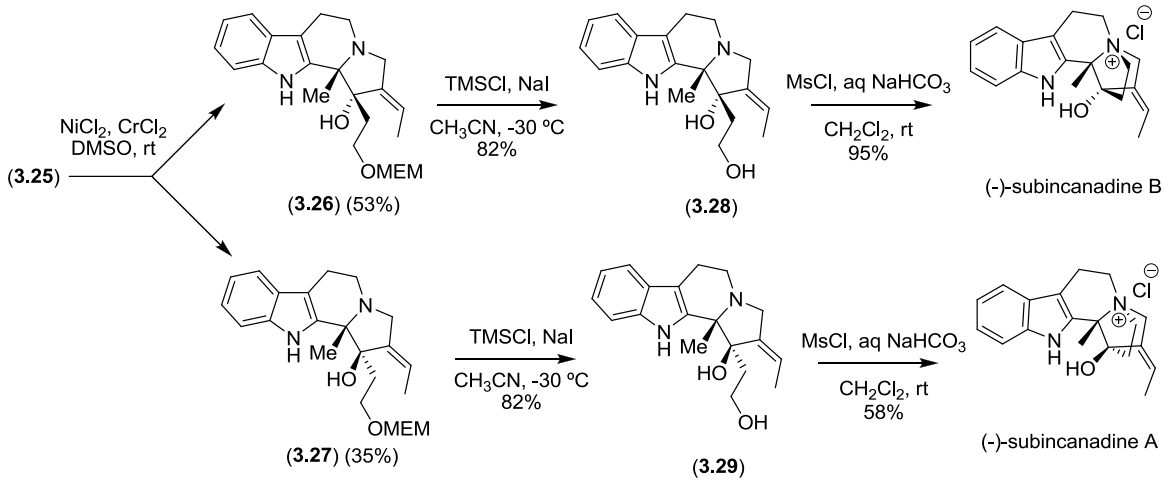
In 2006 Takayama *et al.*[44] published the first asymmetric synthesis of (-)-subincanadine B and (-)-subincanadine A, both in sixteen steps with an overall yield of 2.7%. These syntheses involved an intramolecular diastereoselective Pictet-Spengler cyclisation and an intramolecular Nozaki-Hiyama-Kishi reaction.[45] The syntheses began with the protection of the 1,2-carboxylic acid – alcohol residue of (*S*)-malic acid,[46] followed by the reduction of the free carboxylic acid moiety and formation of *γ*-lactone (**3.14**)[47] (Scheme 3.2). Protection of the secondary hydroxyl group with a *tert*-butyldimethylsilyl protecting group afforded lactone (**3.15**) which was treated with methyl lithium in THF to form the corresponding methyl ketone. The resulting primary alcohol was protected with a pivaloyl group and the TBS protecting group was removed to give (**3.17**).



Scheme 3.2: Synthetic route towards (-)-subincanadines A and B

On reacting methyl ketone (**3.17**) with tryptamine in the presence of CDI, carbonate (**3.19**) was formed which was found to exist in the form of a hemi-aminoacetal in solution. This was able to undergo a diastereoselective Pictet-Spengler reaction in the presence of TMSCl as a Lewis acid to afford Pictet-Spengler product (**3.20**) as a 9:1 mixture of diastereomers. The mixture was recrystallised to give a single diastereomer with an ee of 99% which was used in the remaining steps of the synthesis. The relative stereochemistry was assigned by NOE analysis and it was found that the methyl group and adjacent alkyl chain of the major diastereomer adopted a cis arrangement. This pointed to indole attack of the *in situ* formed iminium ion from the less hindered side, *anti* to the side chain. The synthesis was continued with the removal of the pivaloyl group of the primary alcohol and protection with a MEM ether which would be stable to the strong basic conditions used in the next step. Base hydrolysis of the carbamate and subsequent alkylation of the secondary amine with allylic bromide (**3.23**) afforded iodide (**3.24**). In order to construct the third ring, the primary alcohol was oxidised to ketone (**3.25**) using IBX which was able to undergo the second key step in the synthesis – an intramolecular Nozaki-Hiyama-Kishi reaction (Scheme

3.3). This furnished tetracyclic diastereomers (**3.26**) and (**3.27**) in 53% and 35% yield respectively; the relative stereochemistry of which was assigned by NOE analysis. The synthesis was completed by deprotection of the MEM ether[48] followed by reprotection with MsCl under standard conditions and cyclisation to give the *ent* form of natural subincanadine B and (-)-subincanadine A.

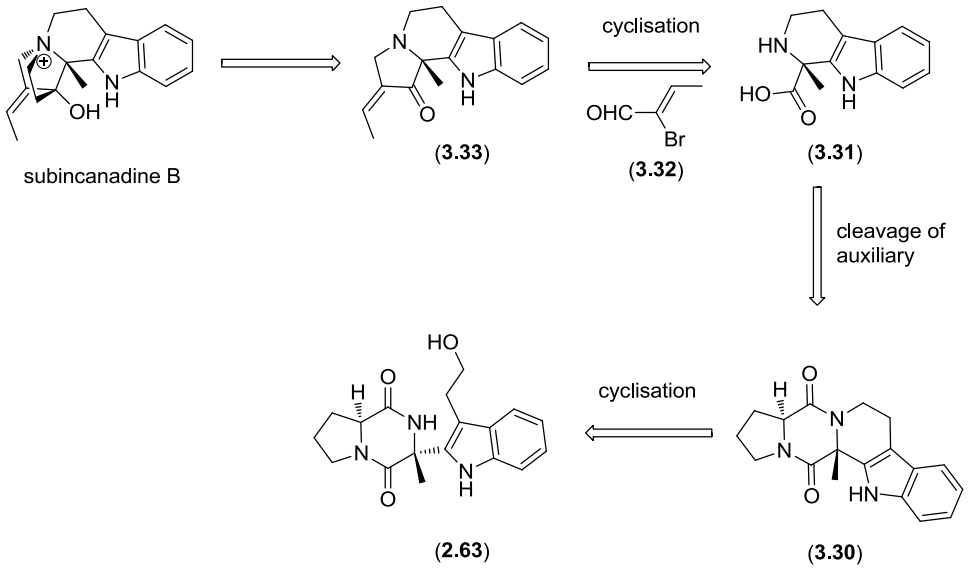


Scheme 3.3: Completion of synthesis of (-)-subincanadines A and B

In the synthesis of subincanadine B by Takayama *et al.* five different alcohol protecting groups were used and 16 synthetic steps were required to furnish the natural product. The chiral quaternary centre was formed in a good diastereomeric ratio of 9:1 but recrystallisation was needed to obtain an enantiomerically pure compound resulting in a poor 47% yield of the key step.

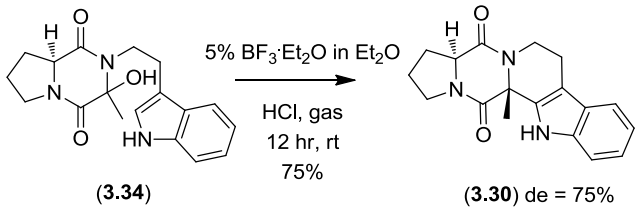
3.2 Concept and Aims

Although subincanadine B had not displayed cyctotoxic activity when tested, its interesting structure rendered it an attractive target for synthesis. It was thought that by using the methodology described in the previous chapter, the quaternary centre of subincanadine B could be constructed by the addition of tryptophol to DKP (**2.53**) to give intermediate (**2.63**) as a single diastereomers (Scheme 3.4). With adduct (**2.63**) in hand, cyclisation of the amide to form fused pentacyclic system (**3.30**) could be achieved. Cleavage of the DKP would regenerate the proline chiral auxiliary and yield amine (**3.31**) which could undergo an alkylation addition with bromide (**3.32**) to provide the required tetracyclic system. Further alkylation would yield subincanadine B.



Scheme 3.4: Retrosynthetic analysis of subincanadine B employing L-proline as a chiral auxiliary

Cyclisation product (**3.30**) had been synthesised previously by Czarnoki *et al.*[49] via a Pictet-Spengler reaction of aminol (**3.34**) to yield product (**3.30**) in a 75% yield and in 75% de (Scheme 3.5).



Scheme 3.5: Pictet-Spengler reaction developed by Czarnoki *et al.*

By employing the methodology outlined in chapter 2 in the synthesis of pentacyclic product (**3.30**), the dr of the cyclised product would be higher than that obtained by Czarnoki *et al.* in their Pictet-Spengler reaction.

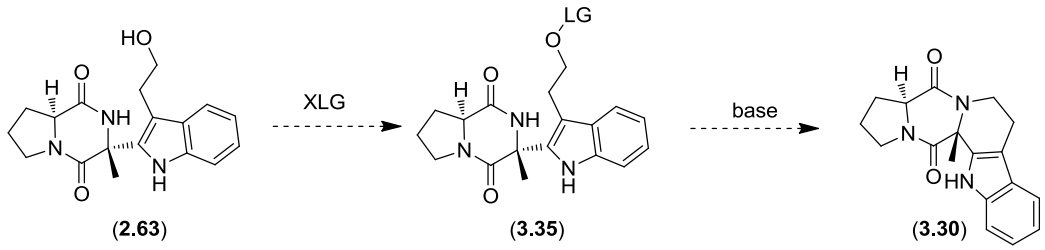
Specifically, the aim of this study was:

1) To apply the methodology developed for the addition of 3-substituted indoles to L-proline derived DKPs to the synthesis of subincanadine B.

3.3 Results and Discussion

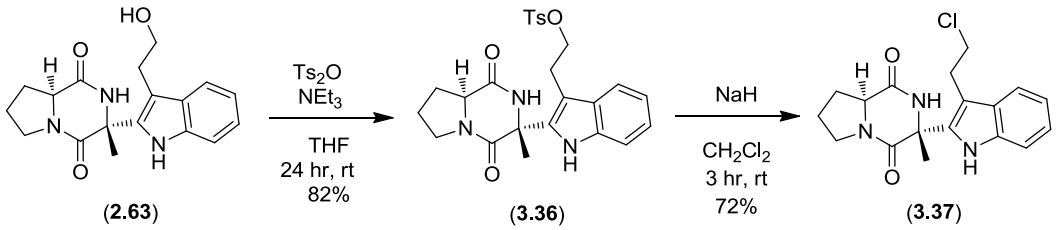
3.3.1 Synthesis of the pentacyclic ring system

The synthesis of the fused pentacyclic ring system from primary alcohol (**2.63**) was thought to be achieved by first creating a leaving group from the primary alcohol, followed by its displacement via an S_N2 reaction with the amide of the DKP (Scheme 3.6).



Scheme 3.6: Synthetic plan towards pentacyclic intermediate (**3.30**)

Initially, tosyl chloride was used to form tosylate (**3.36**) and the desired tosylated product was obtained in a 59% yield. By using tosic anhydride as an alternative tosylating agent, the yield was improved to 82% (Scheme 3.7). With tosylate (**3.36**) in hand, attention was turned to the formation of the fifth cycle by displacement of the newly formed leaving group with the free amide of the DKP. However under basic conditions (NaH), chloride (**3.37**) was afforded in 72% yield as the sole reaction product. It was thought that formation of chloride (**3.37**) was a consequence of using 1M HCl during the aqueous workup (*vide infra*). Attempts were made to use chloride (**3.37**) in the cyclisation reaction with sodium hydride, but chloride proved to be an insufficient leaving group in the intramolecular S_N2 reaction, and only starting material was isolated.



Scheme 3.7: Formation of chloride (**3.37**)

Proof for the absolute stereochemistry for chloride (**3.37**) came from single crystal x-ray diffraction (Figure 3.2). The crystal structure showed, as expected, that the indole moiety was positioned underneath the convex ring system.

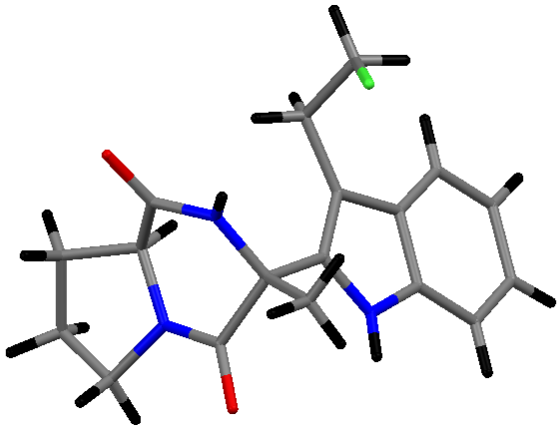
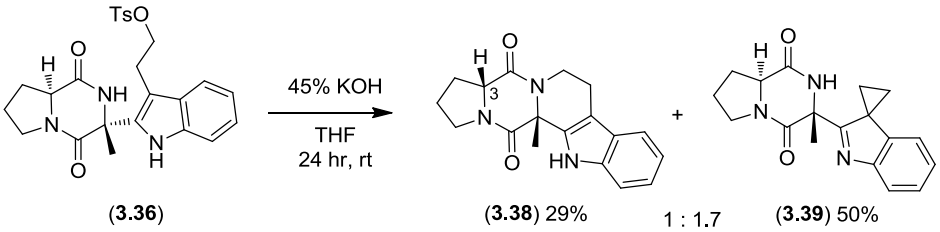


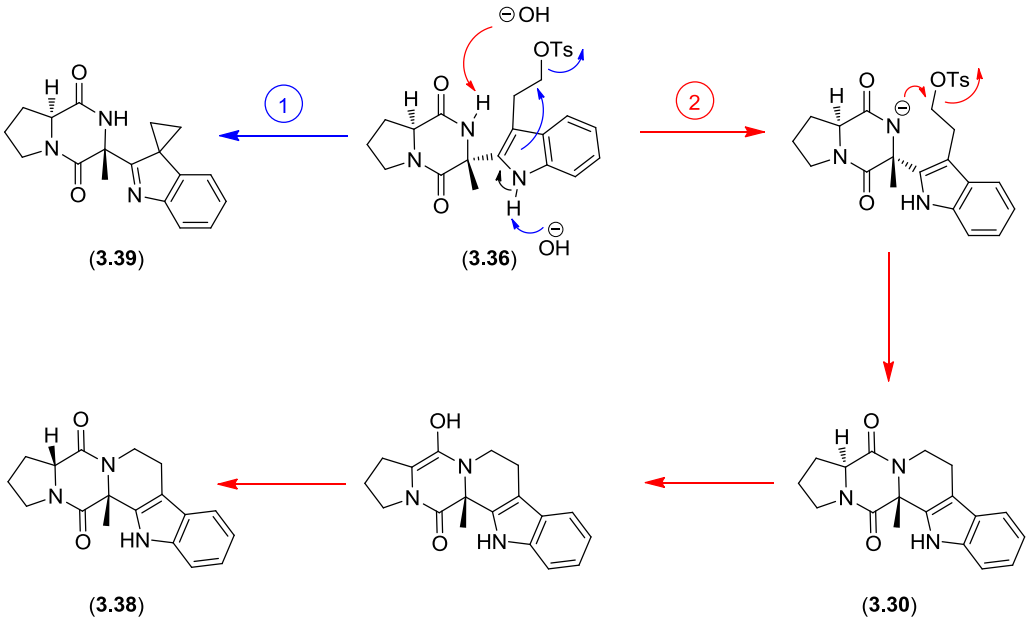
Figure 3.2: X-Ray crystal structure of (**3.37**)

A new approach to prevent chloride formation was to avoid aqueous workup with hydrochloric acid. Pleasingly, under 45% aq KOH conditions, cyclised product (**3.38**) was isolated in 29% yield together with cyclopropane (**3.39**) in 50% yield (Scheme 3.8). It is assumed that cyclopropane (**3.39**) must have been the predominant product in the cyclisation reaction with NaH, (Scheme 3.7) and on workup with hydrochloric acid, the cyclopropane was opened by chloride ions in solution to yield chloride (**3.37**). Cyclisation product (**3.38**) appeared to have epimerised at C-3 under strongly basic conditions. Epimerisation at C-3 of (**3.38**) was previously reported by Czarnocki *et al.*[50] in the presence of sodium methoxide in methanol at room temperature.



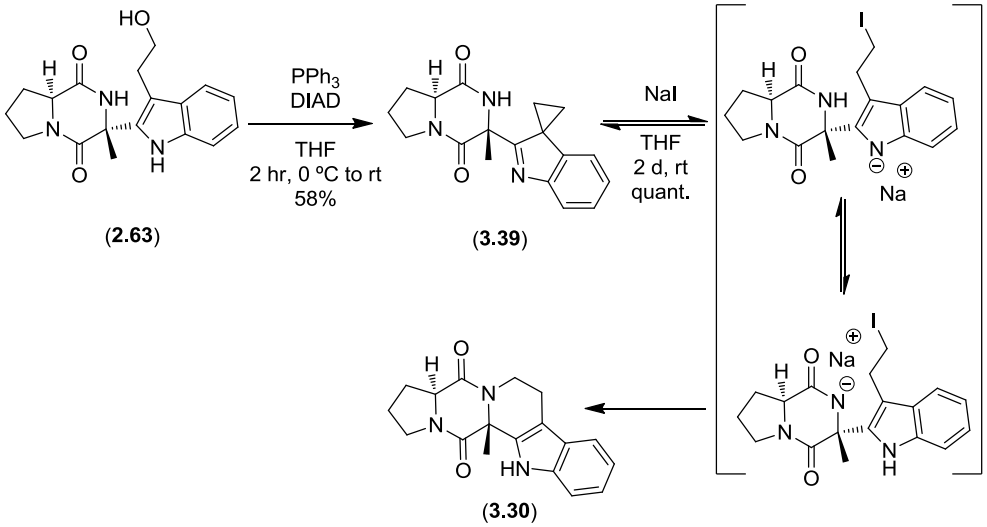
Scheme 3.8: Cyclisation reaction

The reaction was thought to proceed through two competing pathways (Scheme 3.9). The first was deprotonation of the indole N-H and subsequent formation of cyclopropane (**3.39**). The second was deprotonation of the less acidic amide and intramolecular S_N2 displacement of the tosylate to form cyclised product (**3.30**). The change in stereochemistry at position 3 of the DKP is consistent with formation of an enolate under basic conditions followed by reprotonation to form pentacycle (**3.38**) as the thermodynamic product. The larger quantity of cyclopropane (**3.39**) formed compared to cyclised product (**3.38**) suggests that reaction pathway (1) proceeds more rapidly than reaction pathway (2).



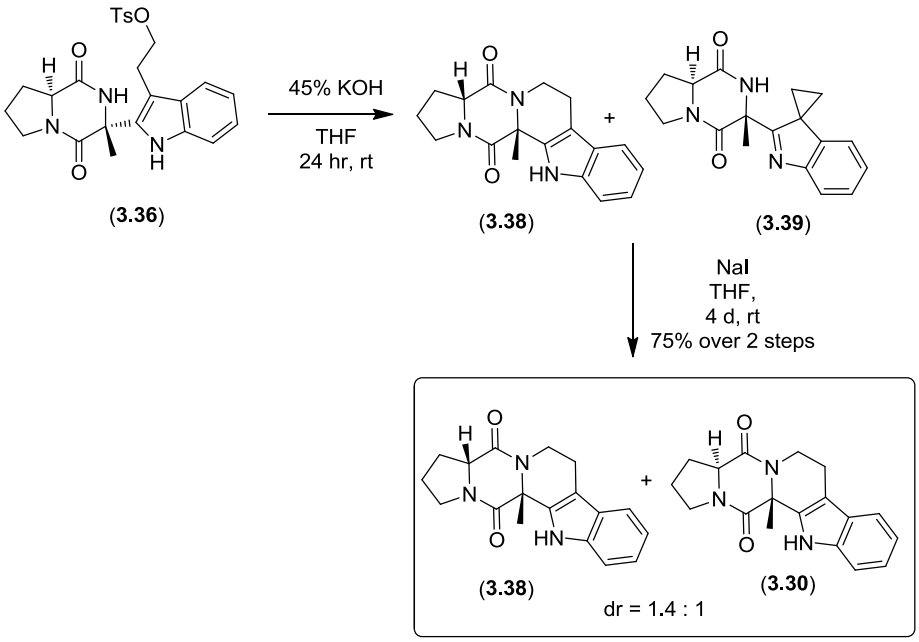
Scheme 3.9: Proposed reaction pathways

In order to investigate the cyclopropane side product further, it was synthesised directly from primary alcohol (**2.63**) via a Mitsonobu[51] reaction in 58% yield (Scheme 3.10). When cyclopropane (**3.39**) was subjected to the same conditions it was formed under (45% aq KOH in THF) no reaction took place as expected. It was proposed that in order to convert cyclopropane (**3.39**) into cyclised product (**3.30**), the cyclopropane ring would have to be attacked by a nucleophile that would open the ring and create a leaving group that could be subsequently displaced by the free amide of the DKP in an intramolecular S_N2 reaction. As chloride had failed to act as a leaving group in the cyclisation reaction, formation of an iodide was attempted as iodide is a better leaving group than chloride. Cyclopropane (**3.39**) was reacted with two equivalents of sodium iodide in THF and after two days at room temperature, cyclised product (**3.30**) was isolated in a quantitative yield. In the absence of base, enolate formation at position 3 was not possible so only the less stable cyclised product (**3.30**) could be formed (Scheme 3.10).



Scheme 3.10: Ring opening of cyclopropane (**3.39**) to form cyclised product (**3.30**)

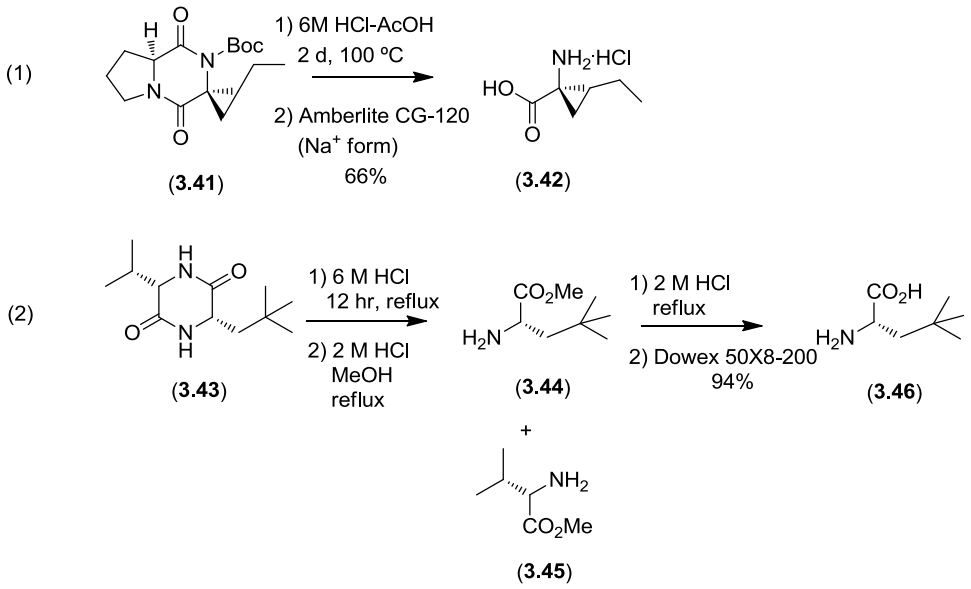
The discovery that sodium iodide could react with cyclopropane (**3.39**) to generate cyclised product (**3.30**) was used in order to increase the yield of cyclised product in the reaction of tosylate (**3.36**) with aqueous potassium hydroxide. After the initial reaction of tosylate (**3.36**) under basic conditions to form a mixture of cyclised material (**3.38**) and cyclopropane (**3.39**), the reaction was worked up and the crude redissolved in THF and sodium iodide added (Scheme 3.11). Cyclised product (**3.38**) present in the crude starting material remained untouched by the sodium iodide and cyclopropane (**3.39**) was completely converted to cyclised product (**3.30**). The two cyclised products were isolated as a mixture of diastereomers in a 1.4:1 ratio in 75% yield over two steps. The epimerisation at C-3 to give rise to two diastereomers was not problematic for the synthesis as the L-proline chiral auxiliary had already been used to form the quaternary centre and would be removed in the following step. Having successfully synthesised cyclised products (**3.38**) and (**3.30**), attention was turned to the cleavage of the DKP.



Scheme 3.11: Formation of diastereomers (**3.38**) and (**3.30**)

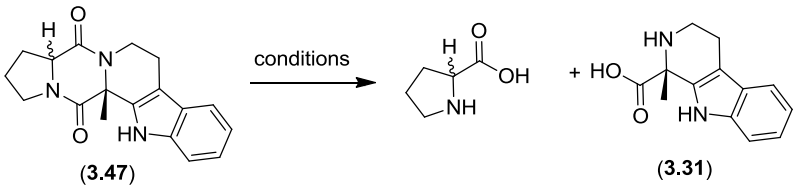
3.3.2 Attempted cleavage of the DKP

DKP's such as the one used in the methodology project described in chapter 2, are routinely cleaved under strong aqueous hydrochloric acid conditions. For example, in the final step of the enantioselective synthesis of (+)-(1*R*,2*S*)-Allocoronamic acid, Bernabé *et al.*[52] cleaved DKP (**3.41**) by refluxing in a mixture of 6 M HCl and acetic acid (Scheme 3.12 (1)). Davies *et al.*[53] used similar conditions (6 M HCl, reflux) in the cleavage of DKP (**3.43**) to afford (S)-γ-methylleucine in 94% yield (Scheme 3.12 (2)).



Scheme 3.12: Cleavage of diketopiperazine units using aq. HCl

Following these literature precedents different concentrations of aqueous hydrochloric acid were used in an attempt to hydrolyse the DKP moiety. Refluxing cyclised product (**3.47**) in 0.25 M HCl for five days resulted in no reaction and only starting material was isolated (Table 3.1 (entry 1)). When the acid concentration was increased to 1 M and refluxed for five days, only decomposed starting material was observed in the crude ^{1}H NMR (entry 2). Milder conditions of 3 M HCl at room temperature were used but no reaction took place. Refluxing 6M HCl conditions (entry 4), as employed by both Bernabé and Davies in their DKP hydrolysis was tried but as expected only decomposition products were observed in the ^{1}H NMR. A variety of other acids were tried (entries 5-9) but each resulted in the recovery of starting material and not the desired hydrolysis products. Even under strong basic conditions (entries 10-12) cleavage did not occur.

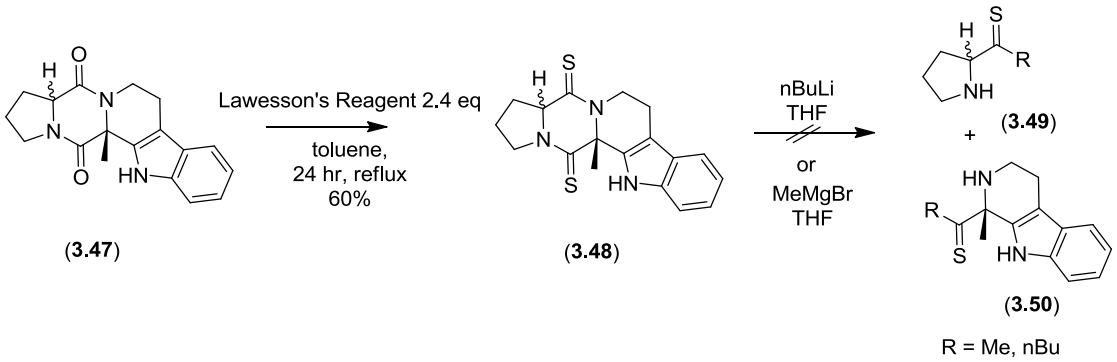


Entry	Reagents	Solvent	Time/days	Temperature	Reaction outcome
1	0.25 M HCl	-	5	reflux	starting material (s.m)
2	1 M HCl	-	5	reflux	no s.m
3	3 M HCl	-	7	rt	s.m
4	6 M HCl	-	2	reflux	-
5	Tf_2O, 5eq DMAP, 3 eq	CH_2Cl_2	4	rt	s.m
6	*p*TsOH, 5 eq	dioxane	7	rt	s.m
7	Amberlyst-15, 5 eq	dioxane	7	rt	s.m
8	TfOH, 5 eq	dioxane	7	rt	s.m

9	Mg, 8 eq $TiCl_4$, 1.5 eq	CH_2Cl_2/THF	2	0 ºC to rt	s.m
10	45% KOH	dioxane	7	rt	s.m
11	45% KOH	dioxane	3	reflux	s.m
12	NaOMe, 10 eq	MeOH	3	rt	s.m

Table 3.1: Conditions screened in an attempt to cleave DKP (**3.47**)

A different approach was tried which involved the manipulation of cyclised product (**3.47**) prior to hydrolysis. Cyclised product (**3.47**), as a 1.4:1 mixture of diastereomers, was converted to thioamide derivative (**3.48**) using Lawesson's reagent as thioamides are better electrophiles than amides. This would increase the susceptibility of the DKP to nucleophilic attack (Scheme 3.13). Organometallic reagents *n*BuLi and MeMgBr were reacted with thioamide (**3.48**) in an attempt to cleave thioamide (**3.48**), but only starting material was recovered.



Scheme 3.13: Synthesis of thioamide (**3.48**) and reaction with organometallic reagents

A diastereomer of thioamide (**3.48**) was crystallised and the absolute stereochemistry of the isolated diastereomer was proved by single crystal x-ray diffraction (Figure 3.3). The epimeric proton α to the thioamide and the methyl group at the quaternary centre were both on the top face of the convex penta-fused ring system.

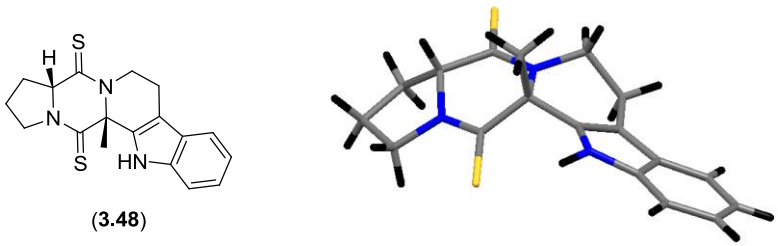
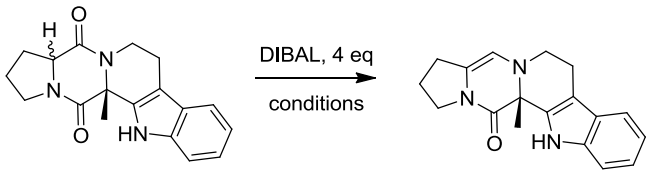


Figure 3.3: X-Ray structure of (**3.48**)

Finally success in the manipulation of pentacycle (**3.47**) was achieved by using DIBAl to reduce the amide adjacent to tertiary stereocentre and form an enamine. The DKP six-membered ring could subsequently be opened by dihydroxylation followed by oxidative cleavage. In the initial reaction with DIBAl, four equivalents were used and the reaction was conducted at -78 ºC in THF for four hours. Only 18% of enamine (**3.51**) was isolated (Table 3.2 (entry 1)). Interestingly, despite the

excess of DIBAl used in the reaction, the amide adjacent to the quaternary stereocentre remained untouched, indicative of its sterically hindered nature. To improve the yield of enamine (**3.51**) the reaction time was reduced to thirty minutes and the yield increased to 56% (entry 2). Changing the solvent to dichloromethane (entry 3) or toluene (entry 4) resulted in a reduced yield of the desired product so THF was employed in the remaining optimisation reactions. Finally by reducing the temperature to -100 ºC and by using 1M HCl in the aqueous workup instead of sodium sulphate decahydrate a clean crude ^{1}H NMR was produced and showed only the presence of product and starting material (entry 5). The reaction time was increased to seven hours at -100 ºC and pleasingly enamine (**3.51**) was isolated in an impressive 93% yield (entry 6).

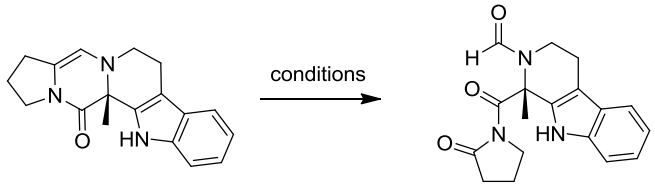


(**3.47**) (**3.51**)

Entry	Solvent	Temperature/ºC	Time/hr	Workup	Yield/%
1	THF	-78	4	$Na_2SO_4.10H_2O$	18
2	THF	-78	0.5	$Na_2SO_4.10H_2O$	56
3	CH_2Cl_2	-78	0.5	$Na_2SO_4.10H_2O$	15
4	toluene	-78	0.5	$Na_2SO_4.10H_2O$	11
5	THF	-100	3	1 M HCl	54
6	THF	-100	7	1 M HCl	93

Table 3.2: Optimisation of enamine (**3.51**) synthesis

With enamine (**3.51**) in hand, conditions were screened to cleave the double bond. Initially *m*CPBA was used to epoxidise the enamine before oxidative cleavage with sodium periodate to give formamide (**3.52**) in 26 % yield (Table 3.3 (entry 1)). Davis oxaziridine was used as an alternative epoxidising agent but after oxidative cleavage with sodium periodate the desired product was produced in a similarly low yield of 27% (entry 2). Finally, using a procedure developed by Jin and co-workers[54] to cleave olefins with osmium tetroxide and sodium periodate, formamide (**3.52**) was produced in a 76% yield after just two hours at room temperature (entry 3).



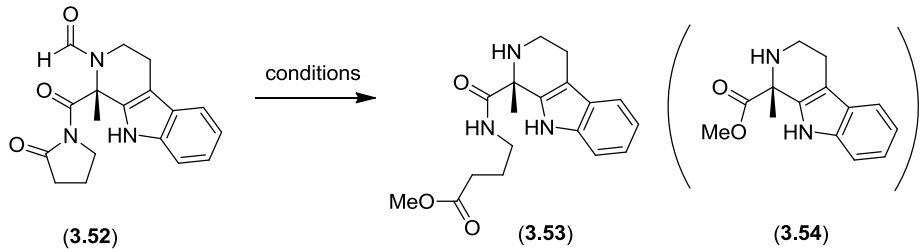
(**3.51**) (**3.52**)

Entry	Reagents	Solvent	Temperature	Time/hr	Yield
1	1) *m*CPBA, 1.1 eq 2) $NaIO_4$, 1 eq	CH_2Cl_2 THF	rt rt	12 12	26%
2	1) Davis oxaziridine 1 eq 2) $NaIO_4$, 1 eq	THF THF	-78 ºC to rt rt	12 12	27%
3	OsO_4, 2.5% Lutidine, 2 eq $NaIO_4$, 4 eq	dioxane:water 3:1	rt	2	76%

Table 3.3: Optimisation of enamine (**3.51**) cleavage

3.3.3 Attempts to form secondary amine (**3.54**)

The remaining task to access key intermediate (**3.54**) in the synthesis of subincanadine B was the hydrolysis of the formamide and removal of the lactam of (**3.52**). Unfortunately, cleavage of the amide to release the lactam was not trivial and hydrolysis attempts employing various concentrations of hydrochloric acid resulted in the ring opening of the lactam to yield amine (**3.53**) instead. As the strength of the acid used was increased, the yield of amine (**3.53**) was found to decrease (Table 3.4 (entries 1-3)). Base hydrolysis was found to be ineffective and only starting material was recovered after reaction with sodium methoxide (entry 4) and potassium hydroxide (entry 5). Attempts to further manipulate amine (**3.53**) were unsuccessful and it appeared that cleavage of the amide bond was not possible due to the poor methyl 5-amino-2-oxopentanoate leaving group.



(**3.52**) (**3.53**) (**3.54**)

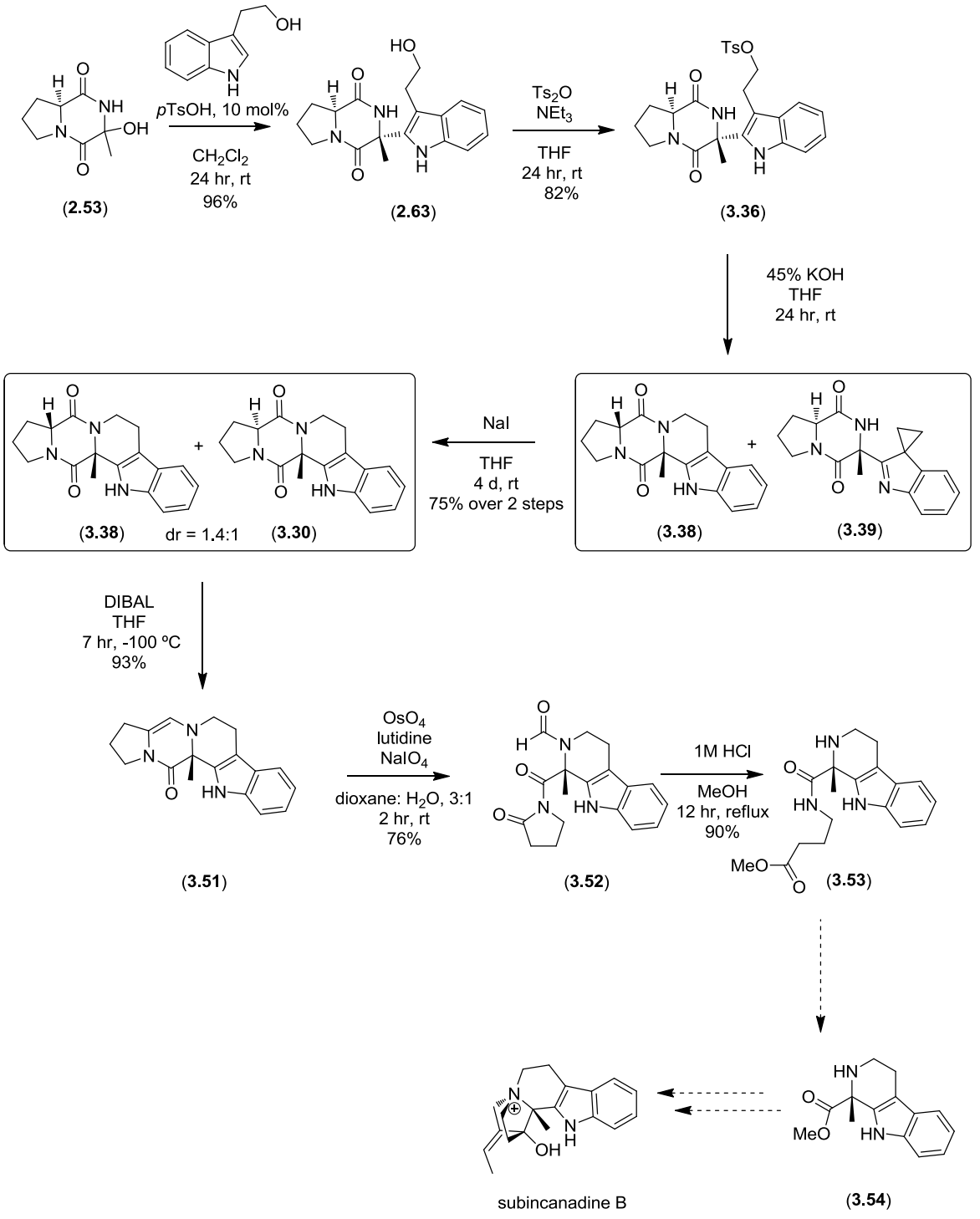
Entry	Regents	Solvent	Temperature	Time	Yield of (**3.53**)
1	1 M HCl	MeOH	reflux	12 hrs	90%
2	3 M HCl	MeOH	reflux	12 hrs	84%
3	6 M HCl	MeOH	reflux	12 hrs	59%
4	NaOMe	MeOH	rt	12 hrs	s.m
5	45% KOH	dioxane	reflux	12 hrs	s.m

Table 3.4: Attempts at formation of (**3.54**)

At this stage in the synthesis the route via DKP (**2.63**) was abandoned and an alternative approach to access subincanadine B was investigated (chapter 5).

3.4 Summary

A new route towards the synthesis of subincanadine B utilising the methodology described in chapter 2 was developed (Scheme 3.14). The synthesis began with iminium ion addition of tryptophol to DKP (**2.53**) to give adduct (**2.63**) in 96% yield as a single diastereomer. The primary alcohol of (**2.63**) was protected as a tosylate to act as a leaving group in the S_N2 reaction with the free amide to form a fused pentacyclic ring system. Cyclised product (**3.38**) was formed in the reaction, together with a cyclopropane by-product (**3.39**). Cyclopropane (**3.39**) was successfully converted to cyclised product (**3.30**) on reaction of the crude reaction mixture with sodium iodide to give a 1.4:1 mixture of diastereomers. These diastereomers were transformed to enamine (**3.51**) in a 93% yield using DIBAl as a reducing agent. Subsequent dihydroxylation with osmium tetroxide and oxidative cleavage with sodium periodate afforded formamide (**3.52**) in 76% yield. On reaction of formamide (**3.52**) with 1 M HCl, amine (**3.53**) was formed which despite attempts could not be transformed to amine (**3.54**).



Scheme 3.14: Attempted synthetic route to subincanadine B

Chapter 4: Phosphoric acid catalysed asymmetric Pictet-Spengler cyclisation

4.1 Introduction

4.1.1 Chiral phosphoric acid catalysis

4.1.1.1 Introduction to phosphoric acids as chiral catalysts

BINOL derived phosphoric acid catalysts were first used by Takahiko Akiyama *et al.* in 2004 in a Mannich type reaction of a ketene silyl acetal with various aldimines.[55] By using *(R)*- or (*S*)- BINOL as a chirality source, and varying the functionalities at the 3 and 3' sites, these bifunctional catalysts possessing both a Lewis basic site and a Brønsted acidic site could be used in reactions to obtain high enantioselectivities[56] (Figure 4.1). The acidity of phosphonates, for example $(OEt)_2P(O)OH$ (pK_a 1.3) are comparable to that of HBF_3 (pK_a -0.44) and are therefore sufficiently acidic to promote acid catalysed reactions.

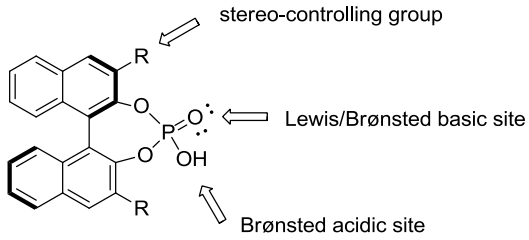
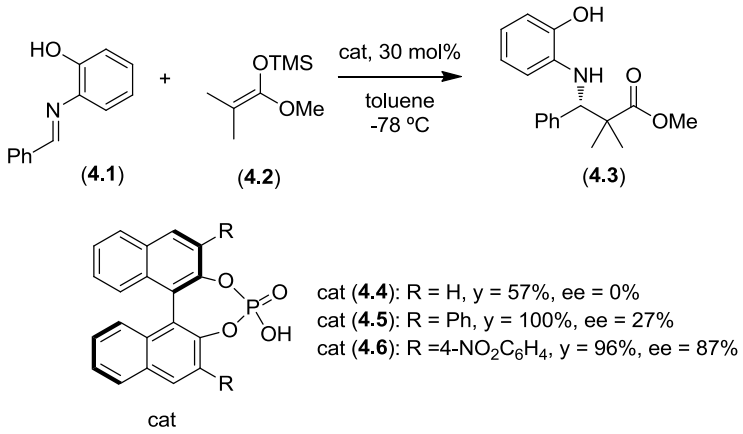


Figure 4.1: Features of chiral phosphoric acid catalysts

Initial studies by Akiyama and co-workers[55] showed that by varying the R group of the phosphoric acid catalyst, the enantioselective outcome of the reaction was greatly affected. For example in the Mannich type reaction of silyl ketene (**4.2**) with aldimine (**4.1**) in the presence of catalyst (**4.4**) (R = H), β-amino ester (**4.3**) was produced as a racemate. By changing the R group to a bulky phenyl substituent the enantioselectivity was improved to 27% which was further increased to an impressive 87% when 4-$NO_2C_6H_4$ was replaced as the R group (Scheme 4.1). These preliminary results suggested that a π-stacking interaction was present in the transition state between the catalyst and the substrates and therefore it was not surprising that the use of catalyst (**4.4**) (an unsubstituted BINOL phosphoric acid) gave β-amino ester (**4.3**) as a racemate.



Scheme 4.1: Enantioselective Mannich-type reaction

A transition structure using a biphenol-derived phosphoric acid catalyst to explain the selectivity was proposed based on experimental results and density functional theory calculations. The transition structure consisted of a cyclic 9-membered zwitterion which only favoured attack from the *Re*-face of the complex due to the steric hindrance associated with the π-stacking interaction of the catalyst R groups and aromatic ring of the aldimine (Figure 4.2).

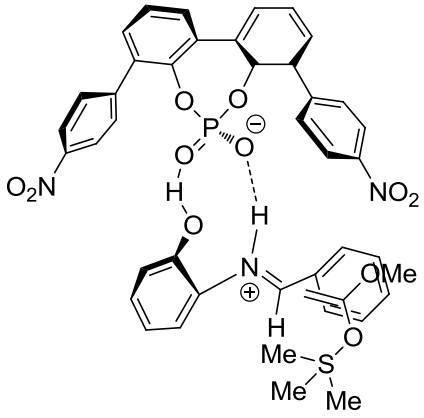
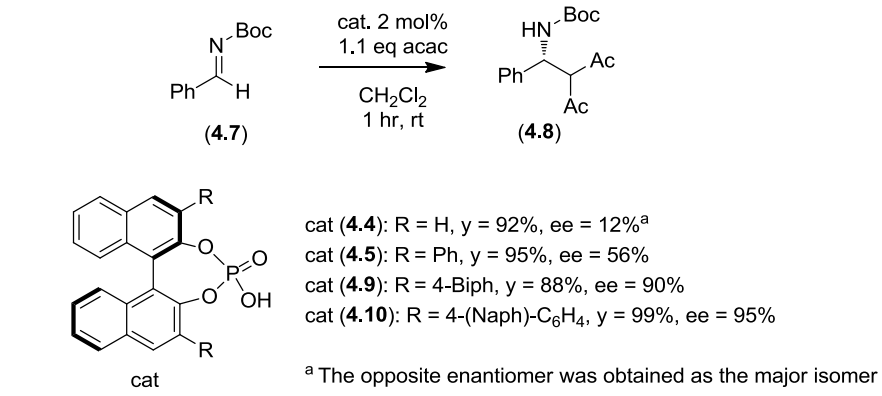


Figure 4.2: Cyclic transition structure to rationalise the observed stereochemistry of the product amine

4.1.1.2 Asymmetric reactions employing chiral phosphoric acid catalysts

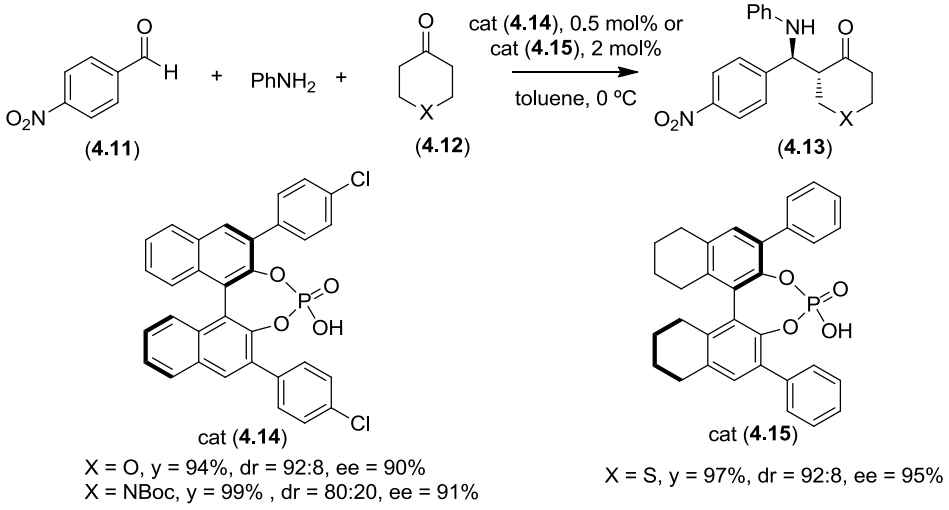
1) Mannich reaction

Terada *et al.* found that chiral phosphoric acids effectively catalysed the addition of acetyl acetone to *N*-Boc imine (**4.7**)[57] (Scheme 4.2). After 1 hour at room temperature β-amino ketone (**4.8**) was produced in a high yield with each of the phosphoric acid catalysts screened. It was found that by increasing the steric bulk at the R position of the catalyst, the enantiomeric excess rose significantly. An ee of 95% was produced when catalyst (**4.10**), possessing an extended π-system, was employed.



Scheme 4.2: Terada's direct asymmetric Mannich reaction

In 2007 this concept was developed further by Gong *et al.* whom reported a phosphoric acid catalysed three-component Mannich reaction.[58] Cyclic derivatives (**4.12**) proved to be successful nucleophiles in their enol form, and by varying the heteroatom in the ring, a variety of β-amino ketones were afforded in excellent yield, dr and ee (Scheme 4.3). Catalyst (**4.14**) was found to give greater enantioselectivities for tetrahydropyran-4-one and piperidin-4-one whereas (*R*)-H_8BINOL derivative (**4.15**) was employed when tetrahydrothiopyran-4-one was used in the reaction. Gong and co-workers proposed that their Mannich reaction proceeded via attack of the aldimine (formed *in situ* from the aldehyde and amine in the presence of the acid), by the enolised cyclohexanone derivative.

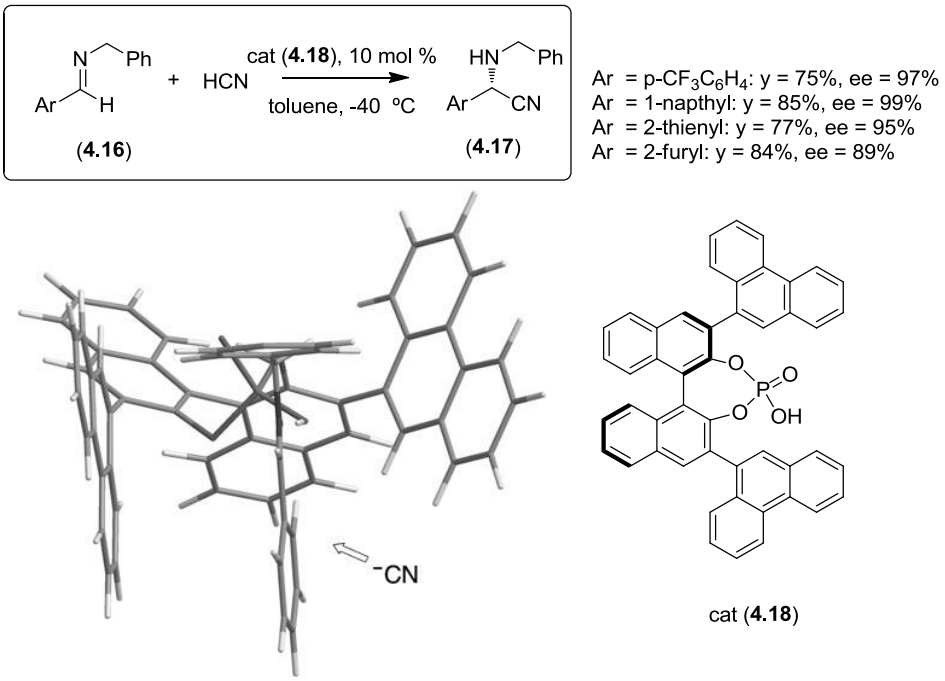


Scheme 4.3: 3-Component Mannich reaction

2) Strecker reaction

Rueping and co-workers developed an asymmetric Strecker reaction using (*R*)-BINOL-derived phosphoric acid catalysts and found, as Terada had found in the asymmetric Mannich reaction, that the use of a bulky catalyst afforded products in the highest enantioselectivities.[59] Catalyst (**4.18**) was found to give impressive ee's when a variety of imines (**4.16**) were reacted with hydrogen cyanide to afford amino nitriles (**4.17**) (Scheme 4.4). A transition structure to explain selectivity was proposed using a crystal structure of cat (**4.18**) and optimisation calculations. This featured

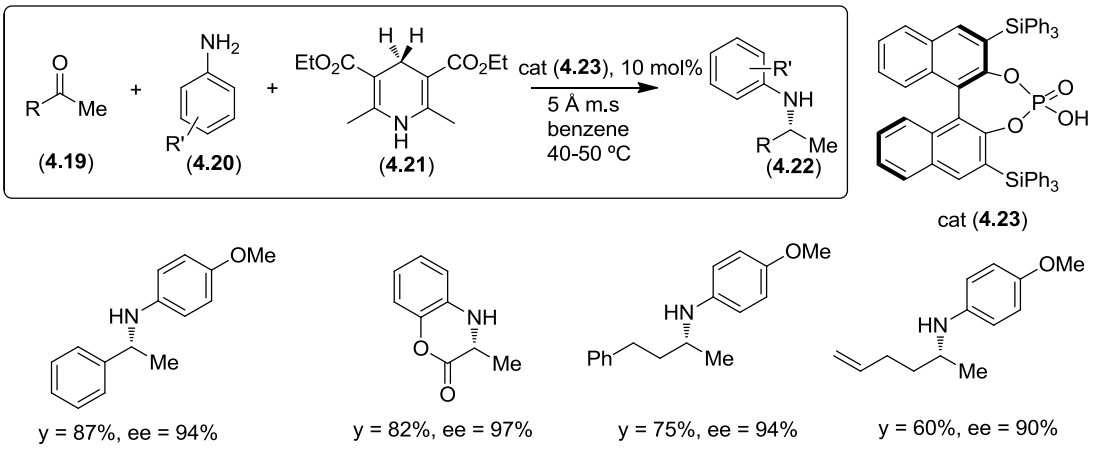
the attack of an iminium ion formed from imine (**4.16**) by the cyanide nucleophile from the less hindered *Re*-face rather than the *Si*-face which was shielded by the phenanthryl group of the catalyst.



Scheme 4.4: Asymmetric Strecker reaction of imine (**4.16**) and transition structure proposed by Rueping and co-workers

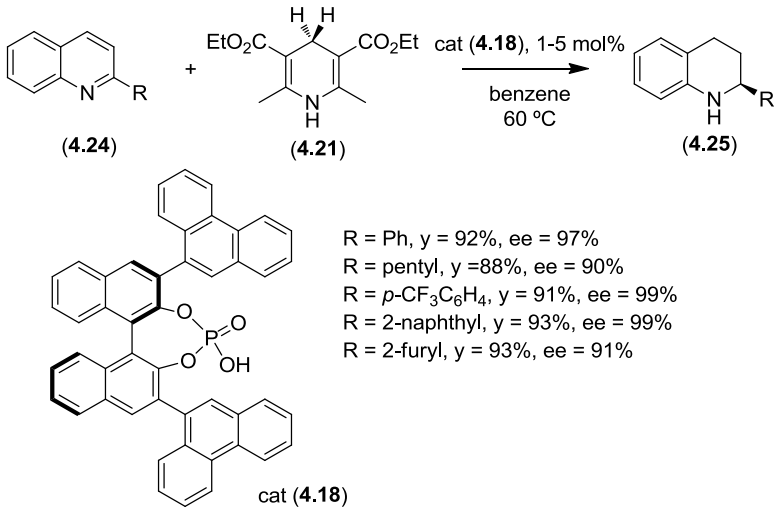
3) Transfer hydrogenations

The creation of chiral amines from achrial pronucleophiles utilising asymmetric phosphoric acid catalysts, as seen in the Strecker reaction, had also been achieved by transfer hydrogenation. MacMillan *et al.* were the first to develop an asymmetric organocatalytic reductive amination reaction involving the use of Hantzsch ester (**4.21**)[60] (Scheme 4.5). Several hydrogen bonding catalysts such as a Jacobsen thiourea and Rawal's taddol were screened but failed to promote the reaction. However, BINOL derived phosphoric acid catalysts proved to be successful catalysts in the transfer hydrogenation reaction and catalyst (**4.23**), developed by MacMillan, facilitated the desired coupling reaction to afford a range of chiral amine products in excellent yield and with impressive enantiomeric excesses.



Scheme 4.5: Organocatalytic reductive amination of aromatic ketones

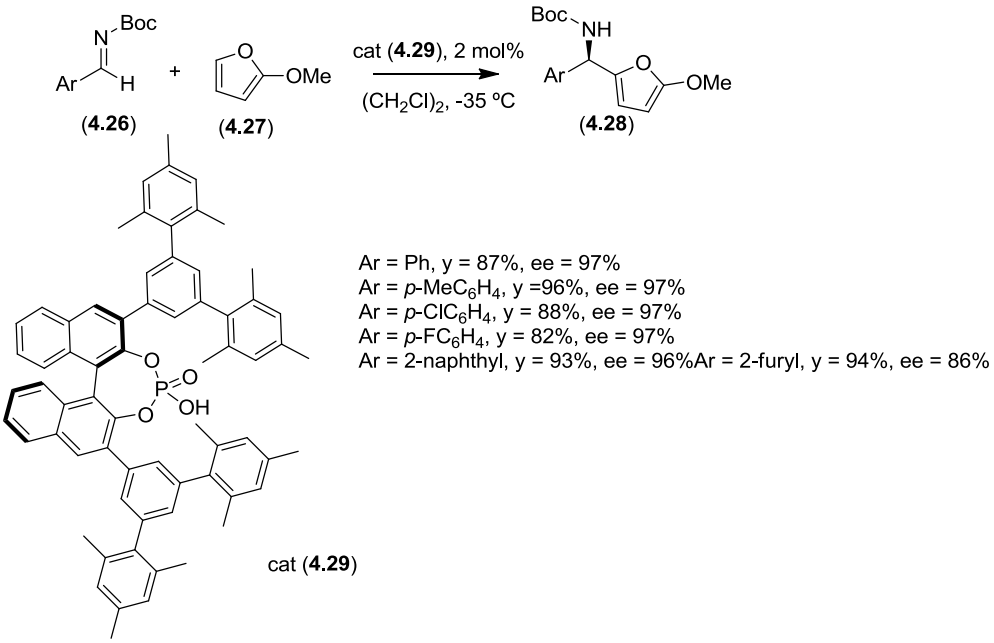
Rueping and co-workers, having previously reported the reduction of imines in the presence of chiral phosphoric acid catalysts using a Hantzsch ester, extended this concept to the reduction of quinolines[61] (Scheme 4.6). By employing bulky catalyst (**4.18**) in the reaction, a series of substituted tetrahydroquinolines (**4.25**) were afforded in high yield and enantiomeric excess.



Scheme 4.6: Transfer hydrogenation of quinolines

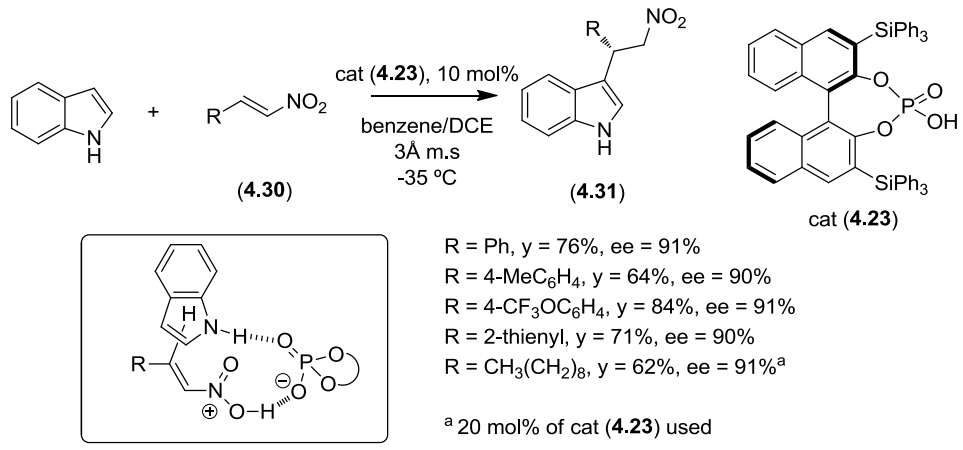
4) Aza Friedel Crafts

Terada and co-workers reported a highly enantioselective aza Friedel Crafts alkylation with *N*-Boc imine (**4.26**) and furan (**4.27**) under asymmetric phosphoric acid catalysis[62] (Scheme 4.7). The nature and positions of the substituents on the aldimine aromatic ring did not greatly influence the enantioselectivity and imines (**4.28**) were produced in high yield and enantiomeric excess.



Scheme 4.7: Aza-Friedel Crafts alkylation using cat (**4.29**)

Akiyama applied the concept of an enantioselective Friedel Crafts reaction to the preparation of 3-substituted indoles from indole and various nitroalkenes (**4.30**).[63] In the presence of phosphoric acid catalyst (**4.23**), Friedel Crafts alkylation products (**4.31**) were afforded in good yield and in excellent enantioselectivity (Scheme 4.8). Interestingly when *N*-Me indole was used in place of indole, the reaction yield decreased significantly and 0% ee was obtained. These observations suggested that a hydrogen bonding interaction between the phosphoryl oxygen atom of the catalyst and the hydrogen atom of the indole N-H was essential for reactivity and to induce enantioselectivity in the product. Based on these findings a nine-membered transition structure was proposed with the phosphoric acid catalyst acting as a bifunctional catalyst.

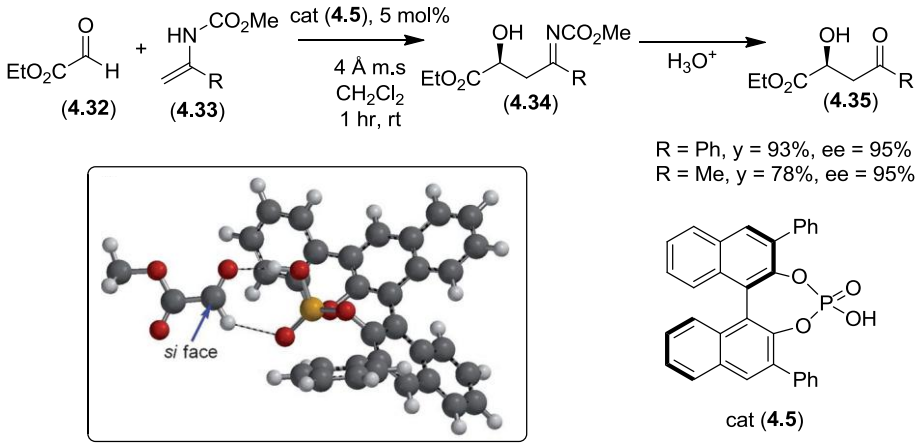


Scheme 4.8: Friedel-Crafts alkylation of indole with nitroalkenes

5) Aza-ene

The activation of carbonyl compounds using chiral phosphoric acids catalysis had been seen previously in a Friedel Crafts reaction developed by Rueping and co-workers. However, examples

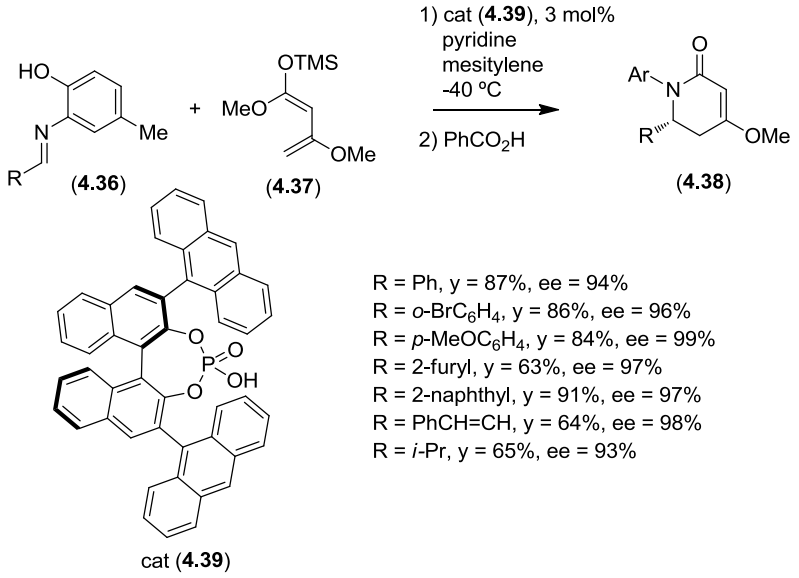
using phosphoric acid catalysts to activate aldehydes were unknown. A novel aza-ene reaction with glyoxylate (**4.32**) and enecarbamates (**4.33**) was investigated by Terada and co-workers and was found to proceed readily in the presence of catalyst (**4.5**)[64] (Scheme 4.9). Hydrolysis of imines (**4.34**) furnished β-hydroxy ketones (**4.35**) in excellent yields and enantioselectivities. A variety of catalysts were screened and it was found that those possessing substituents at the 2', 3', 5' and 6' positions of the phenyl ring were unfavourable in promoting the reaction and governing the stereochemical outcome. In order to rationalise these observations, computational studies were conducted and a transition structure was proposed which showed hydrogen bonding interactions between the aldehyde hydrogen atom and the phosphoryl oxygen atom of the catalyst. From this postulated transition structure it was clear that if the phenyl ring was substituted at the 2', 3', 5' or 6 positions these hydrogen bonding interactions would be prevented. Addition of enecarbamate (**4.33**) to aldehyde (**4.32**) was thought to occur from the *Si*-face of the aldehyde due to the blocking of the *Re*-face by the catalyst phenyl ring.



Scheme 4.9: Aza-ene reaction employing phosphoric acid catalyst (**4.5**)

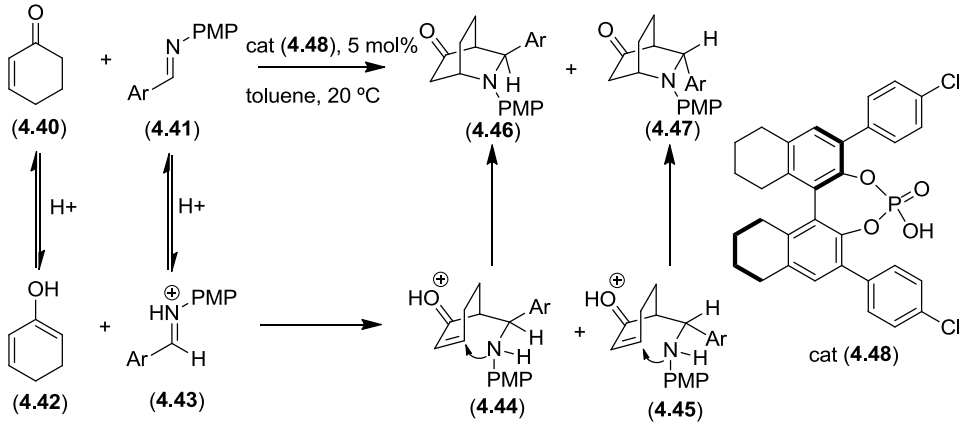
6) Aza Diels Alder

Akiyama[65] developed the first asymmetric Diels Alder reaction of aldimines (**4.36**) with Brassard's diene.[66] Phosphoric acid catalyst (**4.39**) was chosen to promote the reaction and deliver the observed stereochemistry (Scheme 4.10). Initially the reaction was low yielding due to the decomposition of Brassard's diene in the reaction medium. In an attempt to increase the reaction yield, pyridine was used in conjunction with the catalyst to reduce its acidity. This suppressed diene decomposition and resulted in the production of Diels Alder adducts (**4.38**) in high yields and enantioselectivities.



Scheme 4.10: Akiyama's Aza-Diels Alder reaction employing catalyst (**4.39**)

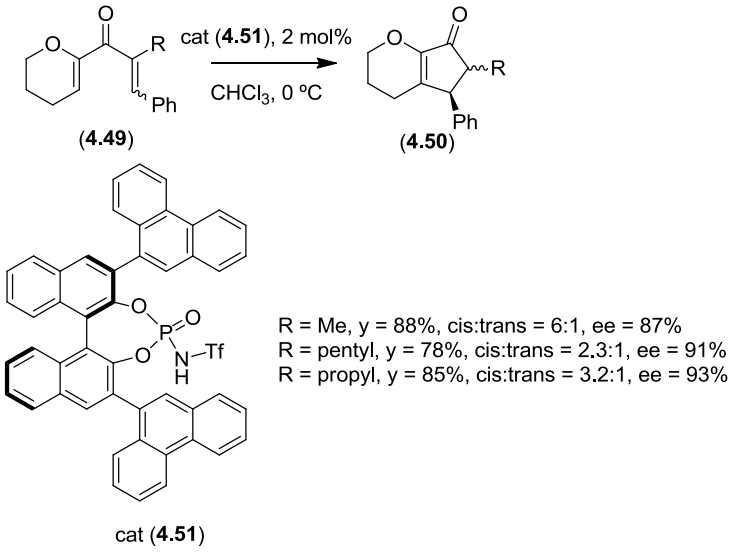
The first direct aza hetero-Diels-Alder reaction using phosphoric acid catalysis was reported by Gong *et al.*[67] shortly after Akiyama's Diels Alder reaction (Scheme 4.10) appeared in the literature. It involved the direct use aldimines (**4.41**) with cyclohexenone (**4.40**) in the presence of chiral phosphoric acid catalyst (**4.48**) to form a range of Diels Alder adducts (**4.46**) and (**4.47**) (Scheme 4.11). It was thought that cyclohexenone (**4.40**) would enolise under the acidic conditions to enol (**4.42**) and undergo a Mannich reaction with the activated aldimine (**4.43**). Newly formed amines (**4.44**) and (**4.45**) would react with the cyclohexenone moiety via an intramolecular 1,4-addition to furnish cyclised adducts (**4.46**) and (**4.47**). A range of differently substituted aromatic aldimines were employed and gave products in good diastereomeric ratios, and in excellent yields and enantioselectivities.



Scheme 4.11: Aza hetero-Diels Alder reaction of cyclohexenone with aldimines (**4.41**)

7) Nazarov cyclisation

A subsequent use of phosphoric acid catalysis in electrocyclic reactions was reported by Reuping *et al.* in their phosphoric acid catalysed Nazarov cyclisation[68] (Scheme 4.12). The reaction could be applied to dienones with alkyl and aryl substituent's to give cyclised products (**4.50**) in moderate selectivity and in excellent yield and enantiomeric excess. *N*-triflyl phosphoramide catalyst (**4.51**)[69] was found to give higher enantiomeric excesses and faster reaction times that the corresponding BINOL phosphoric acid derivative. Replacing the hydroxyl group in the catalyst with a strong electron acceptor group such as NTf, would result in a lowering of the catalyst pKa, and hence a reduction in reaction time. Indeed the pKa of N-triflyl benzamide (pKa 11.06) in acetonitrile was found to be much lower than that of benzoic acid (pKa 20.7).

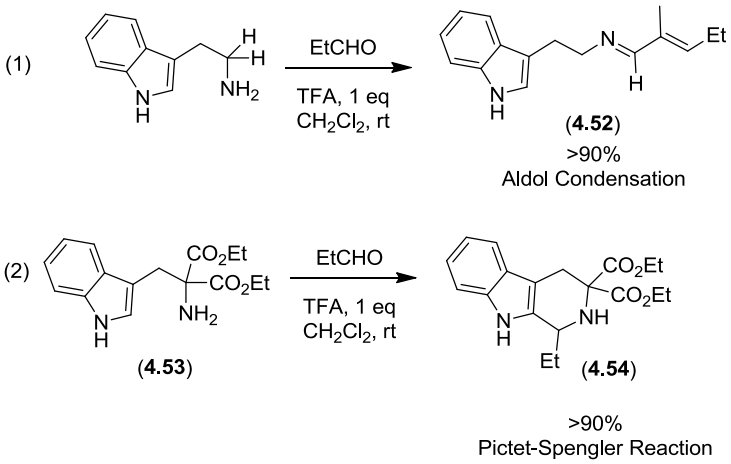


Scheme 4.12: Reuping's Nazarov cyclisation with catalyst (**4.51**)

4.1.2 Enantioselective Pictet-Spengler cyclisation reactions

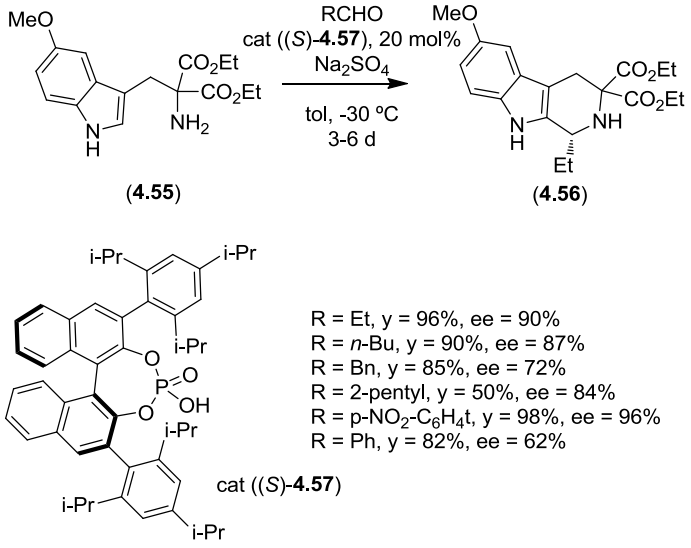
4.1.2.1 Employment of chiral phosphoric acid catalysis

List and co-workers[70] were the first to use BINOL derived phosphoric acid catalysts in an asymmetric Pictet-Spengler[71] reaction. Initially, to probe reactivity, a Pictet-Spengler reaction with tryptamine and propionaldehyde was carried out in the presence of TFA (Scheme 4.13 (1)). However, imine (**4.52**) was the major product of the reaction resulting from homo aldol condensation and imine formation. It was postulated that by using geminally disubstituted tryptamine (**4.53**), reactivity would be increased, suppressing homo aldol condensation, and cyclisation would be favoured due to the Thorpe-Ingold effect[72]. Indeed geminally disubstituted tryptamine (**4.53**), when reacted under the previously tried reaction conditions afforded the desired Pictet-Spengler product as the dominant reaction product (Scheme 4.13 (2)).



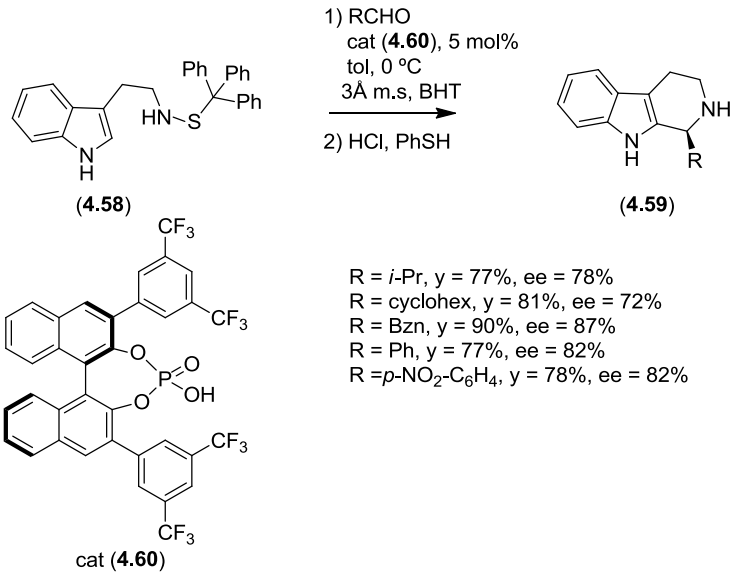
Scheme 4.13: Pictet-Spengler reaction with disubstituted tryptamine

After optimisation of the reaction conditions a variety of aldehydes were screened to expand the reaction scope. It was found that aromatic aldehydes and both branched and unbranched aliphatic aldehydes yielded Pictet-Spengler products in impressive enantioselectivities and yields in the presence of bulky phosphoric acid catalyst ((*S*)-**4.57**) (Scheme 4.14).



Scheme 4.14: The scope of List's enantioselective Pictet-Spengler reaction

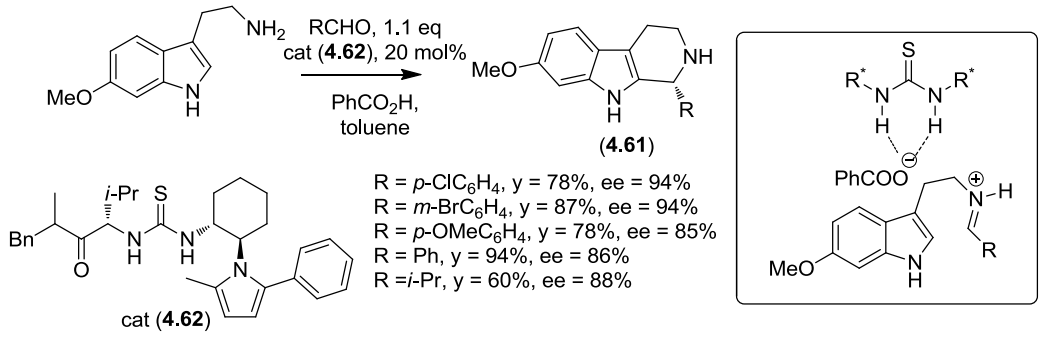
To address the limitation associated with the requirement of using geminally disubstituted tryptamine (**4.53**) to effect a Pictet-Spengler reaction, Hiemstra *et al.*[73] developed a methodology for the preparation of tetrahydro-β-carbolines (**4.59**) from *N*-sulfenyltryptamines (**4.58**) (Scheme 4.15). The role of the sulfenyl substituent was to stabilise the intermediate iminium ion formed and thus promote the Pictet-Spengler reaction. The sulfenyl substituent could be removed at the end of the reaction by stirring with thiophenol in aqueous acid. The reaction was successful and after optimisation of the reaction conditions, the scope of the reaction was explored by employing different aldehydes to generate a series of differently substituted tetrahydro-β-carbolines in excellent yields and enantioselectivities.



Scheme 4.15: Asymmetric Pictet-Spengler reaction using sulfenyl tryptamine (**4.58**)

4.1.2.2 Employment of thiourea derived asymmetric organocatalysts

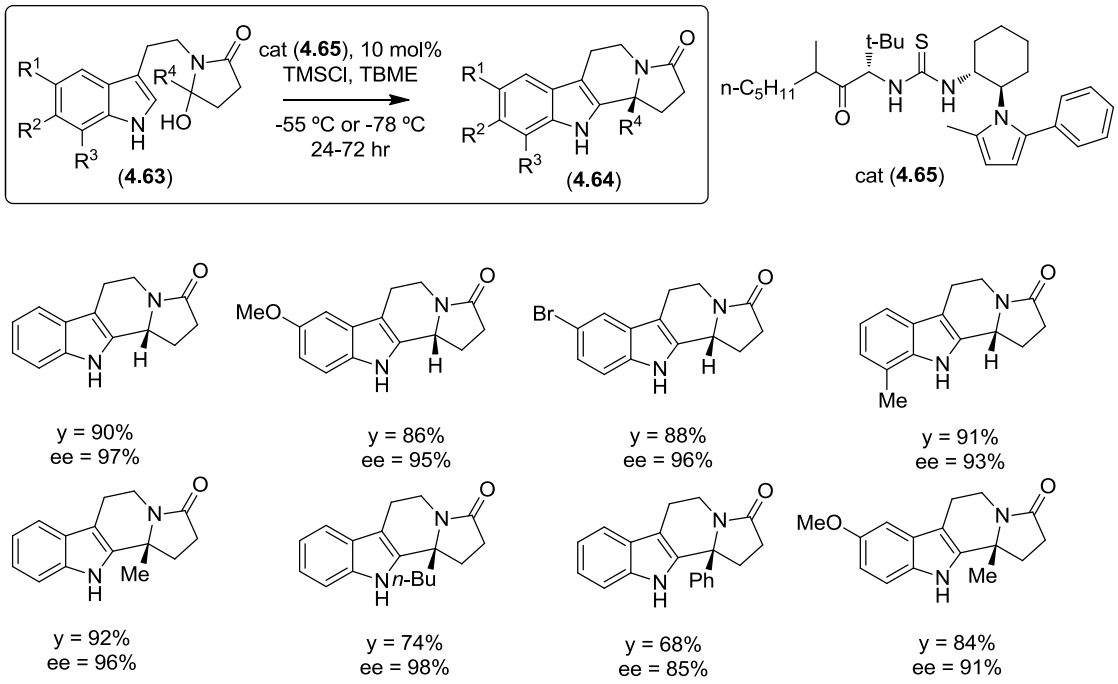
Jacobsen and co-workers[74] found an alternative means of catalysing the reaction between 6-methoxy tryptamine and an aldehyde to yield tetrahydro-β-carbolines. This involved the use of thiourea derived catalyst (**4.62**) (Scheme 4.16). The catalyst was thought to assist in the reaction by forming a hydrogen bond between the thiourea moiety and the conjugate base of a weak Brønsted acid additive, which would allow the free proton to activate the iminium ion towards Pictet-Spengler cyclisation. The acid additive (benzoic acid) proved essential for reactivity when aromatic aldehydes were employed. Aliphatic aldehydes, however, did not require the presence of an acid additive for the reaction to proceed but reaction rate was found to decrease appreciably in its absence. Under optimised reaction conditions a range of aliphatic and aromatic aldehydes were used and yields and ee's were consistently high.



Scheme 4.16: Thiourea catalysed Pictet-Spengler reaction and proposed mode of catalyst activation

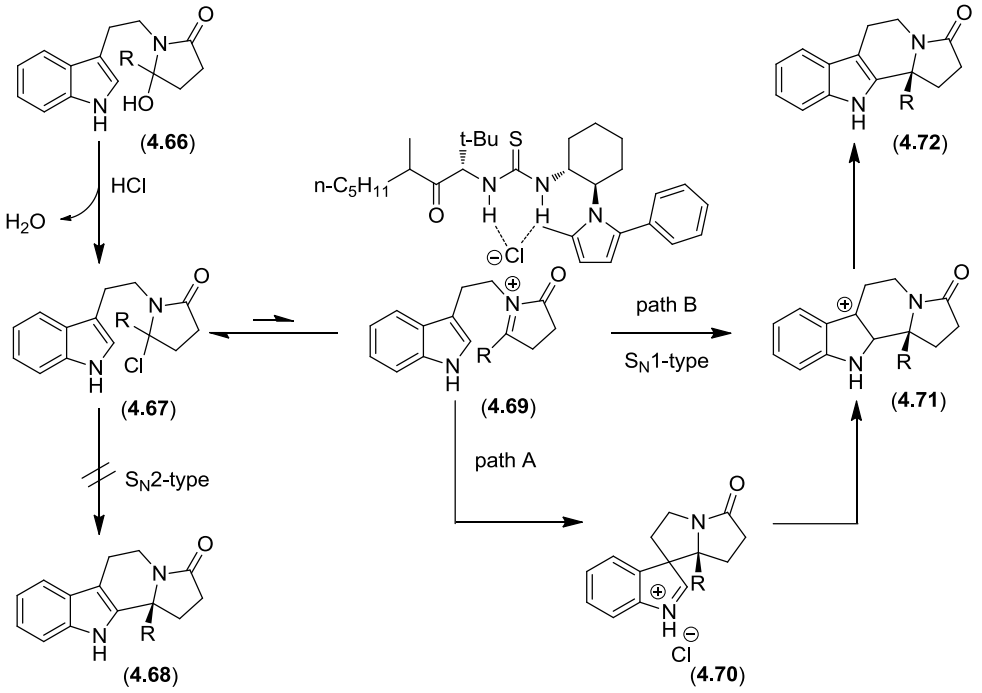
Jacobsen and co-workers had previously investigated the Pictet-Spengler cyclisation of hydroxylactams (**4.63**) using chiral thiourea derived catalyst (**4.65**), in the presence of an acid additive[75] (Scheme 4.17). A thorough screen of acid additives had shown that when

chlorotrimethylsilane was employed, products were formed in high conversion and enantiomeric excess. A selection of hydroxylactams derived from succinimide and glutarimide precursors were cyclised under optimised conditions to furnish a range of Pictet-Spengler products bearing a chiral quaternary centre. The products were obtained in high enantiomeric excess and in excellent yields.



Scheme 4.17: Pictet-Spengler cyclisations of hydroxylactams

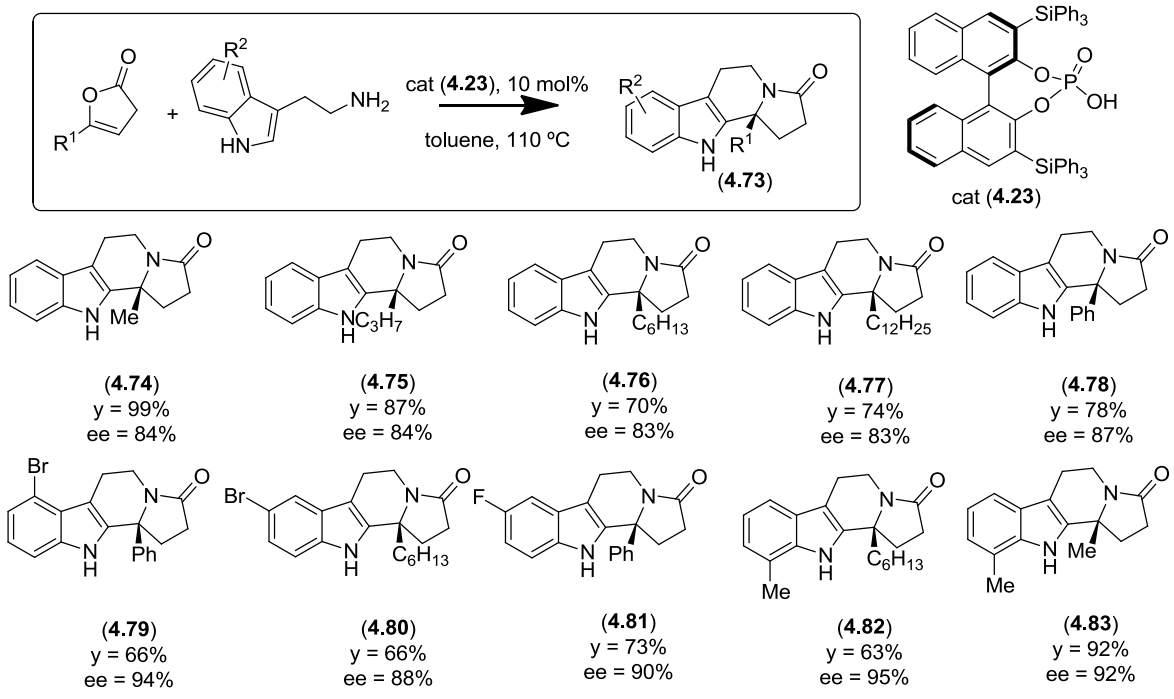
In an effort to understand the reaction mechanism, Jacobsen *et al.* conducted variable temperature ^{1}H NMR experiments and found that chlorolactam (**4.67**)[76] was formed rapidly and reversibly in solution (Scheme 4.18). Cyclisation was thought to occur via an S_N1-type mechanism rather than by an S_N2-type displacement as when R=H, the reaction rate was considerably reduced.[77] The enantio determining step was thought to be either addition of the indole to the lactam to form (**4.70**) or (**4.71**), or collapse of spirocyclic intermediate (**4.70**) to form cyclised product (**4.71**). As (**4.69**) or (**4.70**) did not possess any Lewis basic sites for catalyst association, the catalyst was thought to bind through hydrogen-bonding with the chloride counter ion of iminium (**4.69**). Indeed, pronounced halide counterion effects and solvent effects on enantioselectivity were observed, consistent with the proposed mode of catalyst action.



Scheme 4.18: Proposed reaction mechanism

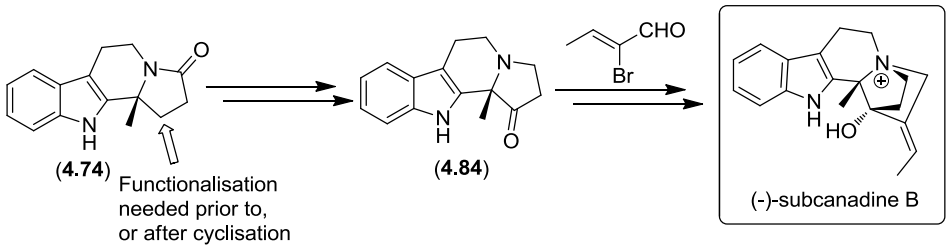
4.2 Concept and Aims

Previous work in the Dixon group by Michael Muratore[78] applied BINOL-derived phosphoric acid catalysis to the Pictet-Spengler cyclisation of hydroxylactams, first introduced by Jacobsen and co-workers.[75] It was found that at elevated temperatures, and in the presence of a BINOL-derived phosphoric acid, tetracyclic products (**4.73**) were afforded in high enantioselectivity and in high yield (Scheme 4.19). The absolute stereochemistry of the cyclised products was determined by single X-ray crystal analysis of 5-bromo product (**4.80**).



Scheme 4.19: Scope of the cyclisation cascade

It was thought that the methodology developed by Michael Muratore could be applied to the synthesis of subincanadine B, providing functionalisation α to the quaternary centre of the Pictet-Spengler product could be introduced prior to, or after cyclisation. If intermediate (**4.84**) could be accessed efficiently using this methodology then further chemical manipulations[79] could furnish (-)-subincanadine B (Scheme 4.20).



Scheme 4.20: Plan to apply methodology to the synthesis of (-)-subincanadine B

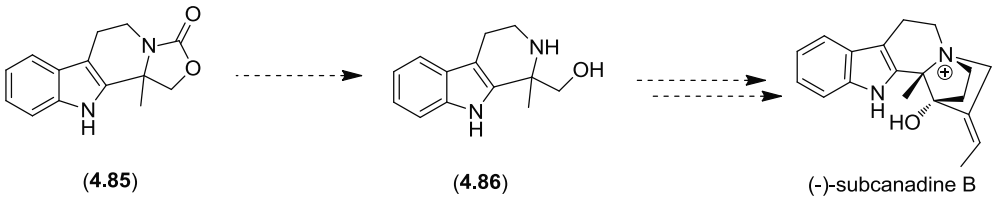
Specifically the aims of this study were:

1) To develop a method to functionalise adjacent to the quaternary centre of the Pictet-Spengler product
2) To discover new methodologies
3) To investigate the reaction mechanism
4) To provide an intermediate that could be used in the synthesis of subincanadine B

4.3 Results and Discussion

4.3.1 Strategy to functionalise α-to the quaternary centre of a cyclised product

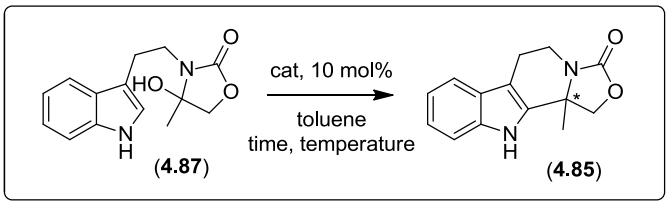
It was necessary to functionalise α-to the quaternary centre of the Pictet-Spengler product in order to provide a substrate which could be manipulated further to give the target, subincanadine B. Investigations began to find a substrate which could undergo an enantioselective Pictet-Spengler cyclisation to afford a cyclised product with functionality adjacent to the quaternary centre. In order for the cyclised product to be used in the synthesis of the target, the ee at the quaternary centre would have to be significant and ideally between 80-90% to allow simple recrystallisation to upgrade the ee. Initial studies focused on the synthesis of oxazolidinone (**4.85**) which could be hydrolysed to give β-amino alcohol (**4.86**), an important intermediate in the synthesis of subincanadine B.

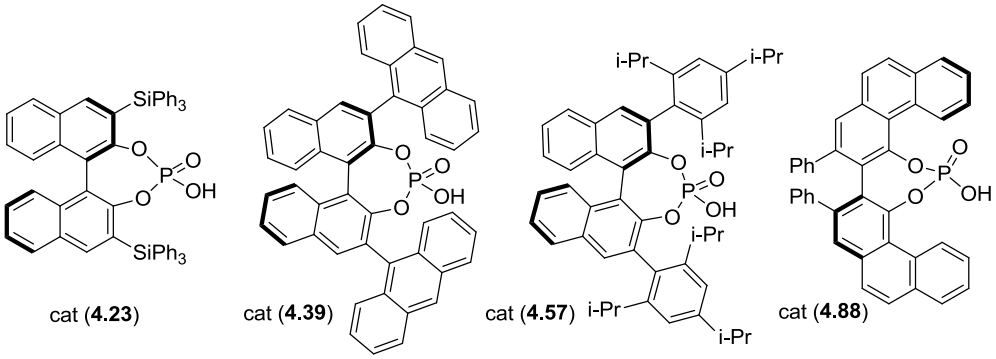


Scheme 4.21: Target structures

4.3.1.1 Enantioselective oxazolidinone (**4.85**) formation

To access the precursor to cyclised product (**4.85**)**,** tryptamine was reacted with hydroxyacetone and CDI to give aminol (**4.87**) in 62% yield. With aminol (**4.87**) in hand, investigations began to obtain cyclised product (**4.85**) in good yield and in high enantiomeric excess (Table 4.1).





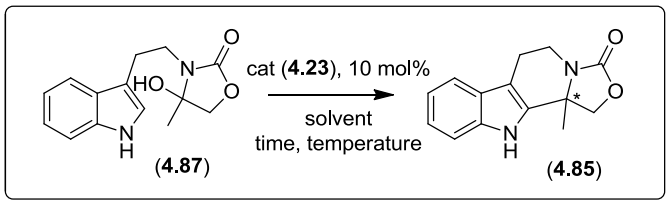
Entry	Catalyst	Temperature	Time/mins	ee/%
1	(**4.23**)	warmed to reflux	60	34
2	(**4.23**)	reflux	15	37
3	(**4.23**)	rt	100	13
4	(**4.23**)	50 ºC	100	18
5	(**4.23**)	70 ºC	15	22
6	(**4.23**)*	reflux	15	33
7	(**4.39**)	reflux	120	10
8	(**4.57**)	reflux	30	30
9	(**4.88**)	reflux	30	36

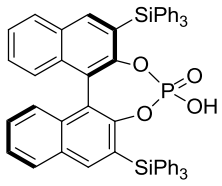
* 4 Å molecular sieves added

Table 4.1: Catalyst and temperature screen in the enantiomeric excess optimisation of oxazolidinone (**4.85**)

Initially, reaction conditions that had been established in the group for Pictet-Spengler cyclisations of hydroxylactams under phosphoric acid catalysis were tried (Table 4.1, entry 1). However, despite the structural similarities between cyclised product (**4.74**) from the previous methodology

and oxazolidinone (**4.85**), the ee of oxazolidinone (**4.85**) was considerably lower (34%), although the reaction yield was comparable (89%). The rate of cyclisation of aminol (**4.87**) was much faster than the rate of reaction between Angelica lactone and tryptamine under the same conditions, so in an effort to improve the enantiomeric excess, which was thought to be affected by temperature, aminol (**4.87**) was added to the reaction mixture only when the solution had reached reflux (entry 2). However, there was not an appreciable increase in enantiomeric excess. A temperature screen was conducted which showed that the lower the reaction temperature, the lower the ee (entries 3-5). It was thought that the reason for the observed decrease in ee with temperature was the reduced ability for water to be driven off in the reaction. In order to test whether water was influencing the enantioselectivity, 4 Å molecular sieves were added to the solution but were found to lower the ee (entry 6). Next a selection of phosphoric acid catalysts bearing different groups at positions 3 and 3' were screened and showed that bulky catalysts (**4.57**) and (**4.88**) (entries 8 & 9) afforded the product in a higher ee than catalyst (**4.39**). However, enantioselectivities still remained low.





cat (**4.23**)

Entry	Catalyst	Solvent	Temperature	Time/mins	ee/%
1	(**4.23**)	heptane	reflux	50	20
2	(**4.23**)	cyclohexane	reflux	50	27
3	(**4.23**)	CH_2Cl_2	reflux	15	9
4	(**4.23**)	THF	reflux	15	8
5	(**4.23**)	mesitylene	reflux	15	44
6	(**4.23**)	xylene	reflux	15	41
7	(**4.23**)	toluene	mw, 200 ºC	15	42
8	(**4.23**)	acetonitrile	mw, 166 ºC	15	18
9	(**4.23**)	DMSO	mw, 200 ºC	15	22
10	(**4.23**)	DME	mw, 200 ºC	15	38
11	(**4.23**)	THF	mw, 200 ºC	15	40

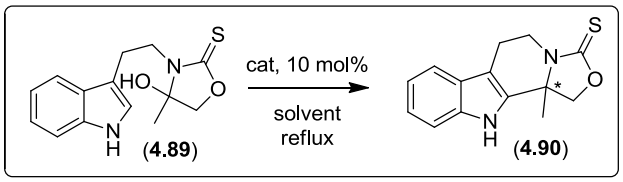
Table 4.2: Solvent screen in the enantiomeric excess optimisation of oxazolidinone (**4.85**)

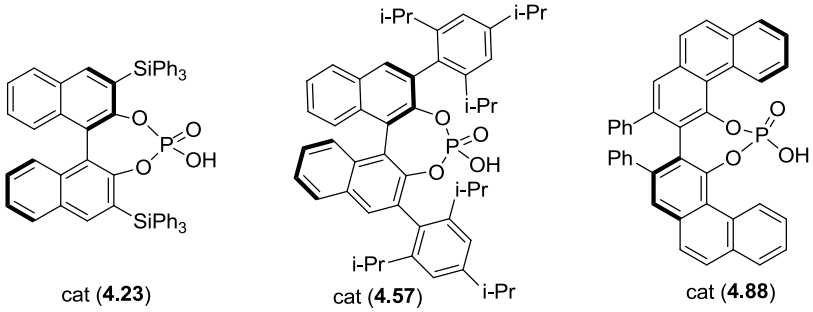
A screen of different solvents showed that solvents such as heptane and cyclohexane were ineffective at promoting high enantiomeric excesses (Table 4.2, entries 1 & 2). Likewise, dichloromethane and THF gave very low ee's (entries 3 & 4). Aromatic solvents such as toluene, mesitylene and xylene gave the highest enantiomeric excesses (37%, 44% & 41% respectively). The solvent screen demonstrated that those solvents which refluxed at a high temperature gave oxazolidinone (**4.85**) in the greatest enantiomeric excess, therefore a series of microwave experiments where it was possible to conduct the cyclisation at elevated temperatures for solvents with low boiling points were carried out (entries 7-11). Interestingly, when THF was heated to 200

ºC the ee increased from 8% (at reflux) to 40%. Toluene and DME also gave reasonable ee's (42% and 38% respectively), however, these ee's were still not high enough to enable recrystallisation of the product to enantiomeric purity, and consequently an alternative approach for generating a cyclisation product which could be used in the synthesis of subincanadine B was explored.

4.3.1.2 Enantioselective oxazolidinethione (**4.90**) formation

From the enantioselectivity optimisation studies conducted on oxazolidinone (**4.85**) formation it seemed that the presence of an oxygen atom in the lactam ring had a detrimental effect on enantioselectivity. An increase in electronegativity around the amide bond of β-carboline (**4.74**) (Scheme 4.19) was obviously not favourable. To address this, the carbamate functionality was replaced by a less electronegative *O*-thiocarbamate. Aminol (**4.89**) was synthesised in a 70% yield from tryptamine, CSI and hydroxyacetone.





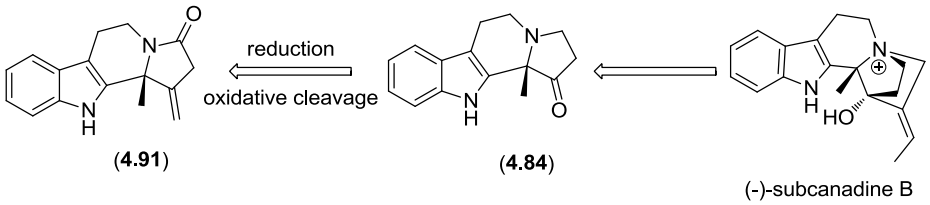
Entry	Catalyst	Solvent	Time/days	ee/%
1	(**4.23**)	toluene	1	3
2	(**4.57**)	toluene	1	18
3	(**4.88**)	toluene	4	11
4	(**4.57**)	CH_2Cl_2	1	12
5	(**4.57**)	THF	7	9
6	(**4.57**)	acetonitrile	1	1
7	(**4.57**)	diethyl ether	1	12

Table 4.3: Enantiomeric excess optimisation of oxazolidinethione (**4.90**)

Initial findings were not as promising as under the standard conditions used in the Pictet-Spengler cyclisations of hydroxylactams, oxazolidinethione (**4.90**) was isolated with an ee of 3% (Table 4.3, entry 1). The employment of bulky catalyst (**4.57**) improved the ee to 18% (entry 2), but even after a solvent screen (entries 4-7) the ee could not be further improved. Having failed to obtain an ee of 80% or greater with oxazolidinone (**4.85**) and oxazolidinethione (**4.90**), a new means of functionalising α-to the quaternary centre of the Pictet-Spengler product was explored.

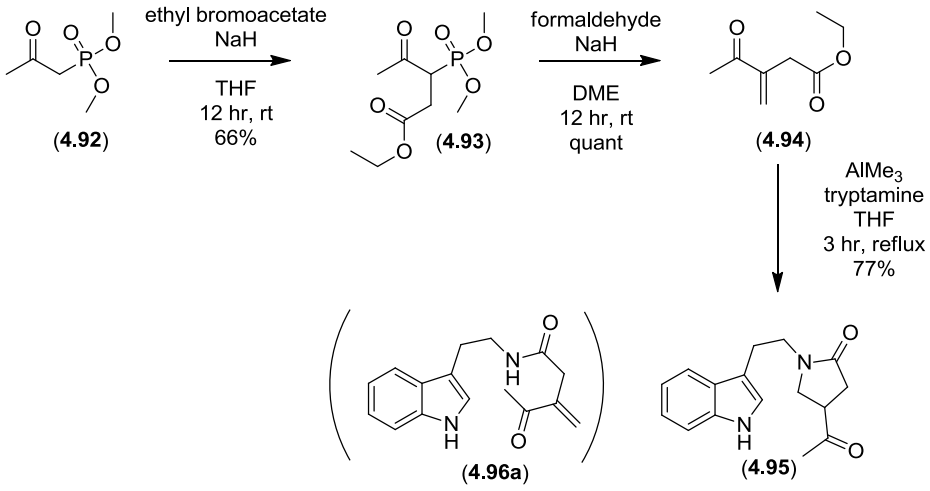
4.3.1.3 Attempted formation of 3-methylene amide (**4.96**)

Instead of introducing functionality α-to the quaternary centre that was contained within the lactam ring, a direct method for functionalising adjacent to the chiral quaternary centre was explored. This method would prove advantageous to that described in sections 4.3.1.1 and 4.3.1.2 as the 5-membered lactam ring, which is a feature of subincanadine B, would remain intact. In order to synthesise subincanadine B using an enantioselective Pictet-Spengler cyclisation it seemed necessary to access intermediate (**4.84**), which had been prepared by Zhai *et al.* in their synthesis of subincanadine B.[42] An obvious first approach would be to synthesise terminal alkene (**4.91**), reduce the amide functionality and introduce the desired ketone through an oxidative cleavage (Scheme 4.22).



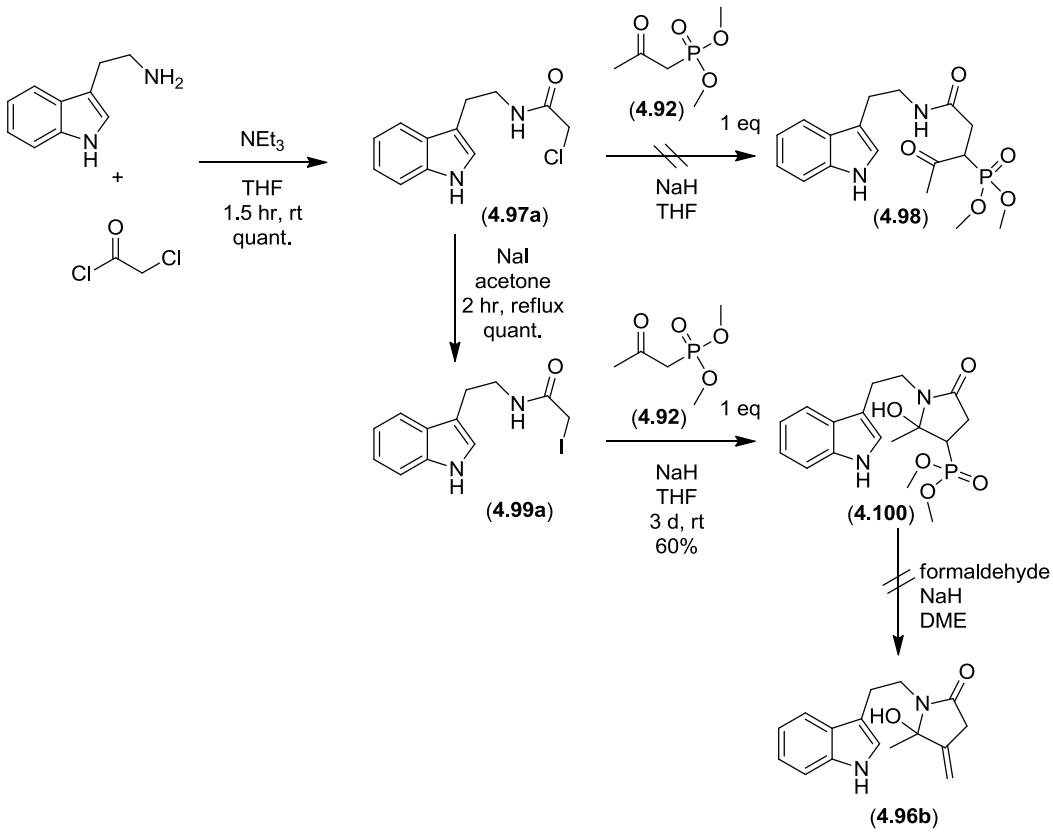
Scheme 4.22: Retrosynthetic plan to ketone (**4.84**)

The synthetic route towards the desired Pictet-Spengler precursor (**4.96a**) is outlined below (Scheme 4.23). It began with the alkylation of phosphonate (**4.92**) with ethyl bromoacetate to afford ethyl ester (**4.93**) in 66% yield.[80] A high yielding Horner-Wadsworth-Emmons[81] reaction provided α,β-unsaturated ketone (**4.94**) which was reacted with tryptamine in the presence of Lewis acid $AlMe_3$ in an attempt to form amide (**4.96a**). However, tryptamine underwent a 1,4-addition reaction with the α,β-unsaturated ketone, instead of directly attacking the ketone, and lactam (**4.95**) was isolated in 77% yield.



Scheme 4.23: Synthetic strategy to 3-methylene amide (**4.96a**)

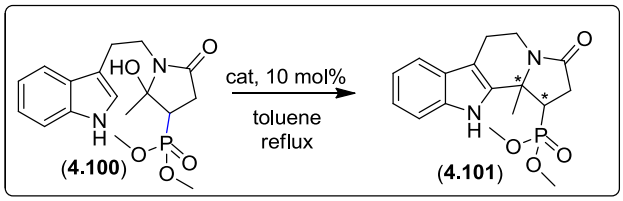
In order to control the reactivity of tryptamine, a new synthesis of the desired product (**4.96**) was tried and tryptamine was incorporated at the beginning of the synthesis. Tryptamine was reacted with chloroacetyl chloride to give chloride (**4.97a**)[82] in a quantitative yield (Scheme 4.24). However, this proved to be unreactive when exposed to phosphonate (**4.92**) under basic conditions. It seemed that a chloride ion was not a good leaving group and so it was substituted for iodide by means of a Finkelstein reaction.[83] Iodide (**4.99a**) was reacted with phosphonate (**4.92**) to give aminol (**4.100**) in 60% yield. Unfortunately attempts to convert the phosphonate group in aminol (**4.100**) to a terminal alkene via a Horner-Wadsworth-Emmons reaction failed.

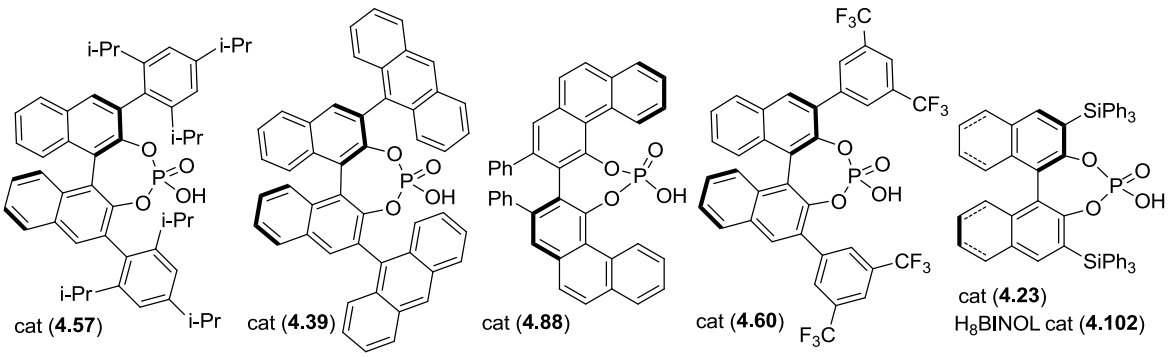


Scheme 4.24: Synthesis of phosphonate aminol (**4.100**)

4.3.2 The development of a diastereoselective Pictet-Spengler cyclisation

Instead of introducing an exo methylene onto the lactam ring prior to cyclisation, it was thought that a Horner-Wadsworth-Emmons reaction could be tried after cyclisation. A cyclisation reaction of this type had not been tried previously and it was hoped that in the presence of a chiral phosphoric acid catalyst, the two adjacent stereogenic centres would be formed with high enantio- and diastereomeric control. Pleasingly, when aminol (**4.100**) was subjected to standard Pictet-Spengler cyclisation conditions, it cyclised to give phosphonate (**4.101**) in an impressive 83% ee, as a single diastereomers (Table 4.4 entry 1). To be able to control the formation of two stereocentres in a Pictet-Spengler cyclisation, one of which was a quaternary centre, was worthy of further investigation.





Entry	Catalyst	Catalyst conc/mM	Temperature	Time/days	ee/%
1	(**4.57**)	7.2	reflux	1	83
2	(**4.39**)	7.2	reflux	1	42
3	(**4.88**)	7.2	reflux	7	18
4	(**4.60**)	7.2	reflux	1	67
5	(**4.23**)	7.2	reflux	1	16
6	(**4.102**)	7.2	reflux	1	7
7	(**4.57**)	7.2	20 ºC	7	-
8	(**4.57**)	7.2	50 ºC	7	88
9	(**4.57**)	7.2	70 ºC	2	86
10	(**4.57**)	13.6	reflux	1	82
11	(**4.57**)	4.8	reflux	1	86
12	(**4.57**)	3.4	reflux	1	83
13	(**4.57**)	2.7	reflux	1	83

Table 4.4: Enantiomeric excess optimisation of phosphonate (**4.101**)

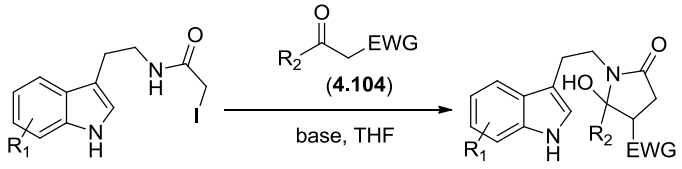
A series of optimisation experiments were conducted, starting with a catalyst screen. However, despite testing a further five catalysts possessing different electronic and steric properties, a higher enantiomeric excess was not achieved (entries 1-6). A screen of temperature showed that a lower temperature than 110 ºC was favourable for ee but resulted in an increased reaction time (entries 7-9). At 20 ºC, however, the reaction did not proceed due to lack of catalyst and substrate solubility. A concentration screen was conducted subsequently (entries 10-13) and ee was found to rise as the concentration of the catalyst decreased, until an optimal concentration of 4.8 mM (86% ee). Below this concentration the ee decreased to 83% and became independent of catalyst concentration.

Having obtained phosphonate (**4.101**) in good enantioselectivity, the removal of the phosphonate group and replacement with a terminal alkene was attempted using LDA to deprotonate α-to the chiral quaternary centre, followed by the addition of paraformaldehyde in a Horner-Wadsworth-Emmons reaction. However, only starting material was isolated. It was thought that a different

functional group in place of the phosphonate could be manipulated to provide a suitable substrate to use in the synthesis of subincanadine B.

4.3.2.1 Exploring the scope of the methodology

To probe the reaction scope a series of aminols bearing electron withdrawing groups α-to the quaternary centre were prepared from iodide (**4.103**) and variously substituted ketones (**4.104**)[84] under basic conditions (Table 4.5). Those aminols with longer alkyl chains at R_2 (entries 5 & 6) gave lower yields than those with methyl groups at R_2, for example phosphonate (**4.100**) (entry 1) was obtained in a 60% yield compared to phosphonate (**4.110**) with a pentyl chain at R_2 which was afforded in a 34% yield. Likewise, those aminols with longer alkyl chains attached to the EWG such as aminol (**4.108**) (entry 4) were obtained in a lower yield than the corresponding aminol with shorter alkyl chains (aminol (**4.107**) entry 3). This was probably due to the steric hindrance associated with the formation of a lactam with bulky groups adjacent to each other.



(**4.103**) (**4.105**)

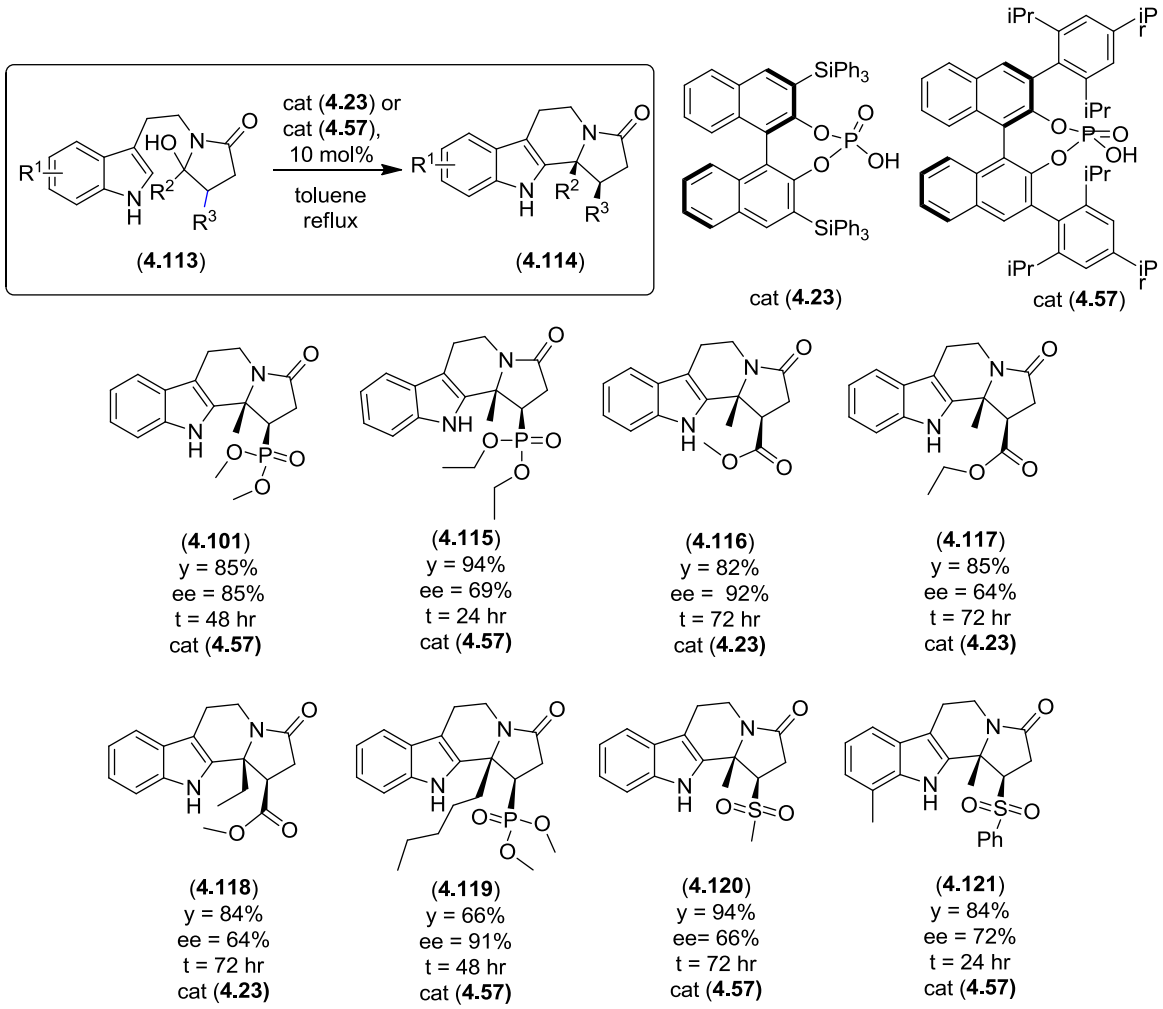
Entry	Compound no.	R_1	R_2	EWG	dr	Yield
1	(**4.100**)	H	Me	$P(O)(OMe)_2$	single diastereomer*	60%
2	(**4.106**)	H	Me	$P(O)(OEt)_2$	9.5:1	40%
3	(**4.107**)	H	Me	CO_2Me	3:1	56%
4	(**4.108**)	H	Me	CO_2Et	1:7	38%
5	(**4.109**)	H	Et	CO_2Me	1:2	43%
6	(**4.110**)	H	n-pentyl	$P(O)(OMe)_2$	-**	34%
7	(**4.111**)	H	Me	SO_2Me	single diastereomer*	62%
8	(**4.112**)	7-Me	Me	SO_2Ph	3:1	89%

***** Purification by trituration only afforded one diastereomer. ** Compound isolated in open chain form, not as an aminol.

Table 4.5: Prepared aminols

With aminols (**4.105**) in hand, a series of Pictet-Spengler reactions were carried out using the optimised reaction conditions for phosphonate (**4.101**). Products were obtained as single diastereomers and in good yield. However, not all substrates were found to give good ee's in the presence of TIPS catalyst (**4.57**), which gave the highest ee for phosphonate (**4.101**), so catalysts were screened for each aminol. The catalysts which gave the greatest enantiomeric excesses were triphenyl silyl catalyst (**4.23**) and TIPS catalyst (**4.57**). The best enantiomeric excess obtained for each substrate is given below (Scheme 4.25). Enantiomeric excesses tended to be influenced by

the size of the substituent α to the quaternary centre which can be seen by comparing the ee of ethyl phosphonate (**4.115**) (ee= 69%) with that of the methyl analogue (**4.101**) (ee = 85%). This observation is consistent with the enantiomeric excesses observed for ethyl ester (**4.117**) (ee = 64%) and methyl ester (**4.116**) (ee = 92%). It appeared from the enantiomeric excesses obtained for cyclised methyl esters (**4.116**) and (**4.118**) that a large alkyl group at the quaternary centre lead to a reduction in ee. However, this was not the case for phosphonate products (**4.119**) and (**4.101**), where a pentyl chain at the quaternary centre resulted in a larger ee than a methyl group at the quaternary centre (91% ee c.f 85% ee, respectively). In the work conducted by Michael Muratore on the Pictet-Spengler cyclisations of hydroxylactams, it was observed that by using 7-methyl tryptamine in the cyclisation, higher enantiomeric excess could be obtained (Scheme 4.19). This could explain the larger ee observed for phenylsulfone (**4.121**) with a methyl group at position 7 on the indole ring, compared to methylsulfone (**4.120**) despite the smaller size of the methylsulfone functionality.



Scheme 4.25: Methodology scope

In order to determine the relative stereochemistry of the cyclised products, NOE experiments were conducted on phenylsulfone (**4.121**) and showed that H-4a, H-9 (Me) and H-6b were on the same face of the molecule while H-7 and H-6a were on the opposite face (see appendix 8). From this it was deduced that the methyl group and the phenylsulfone were *syn* (Figure 4.3).

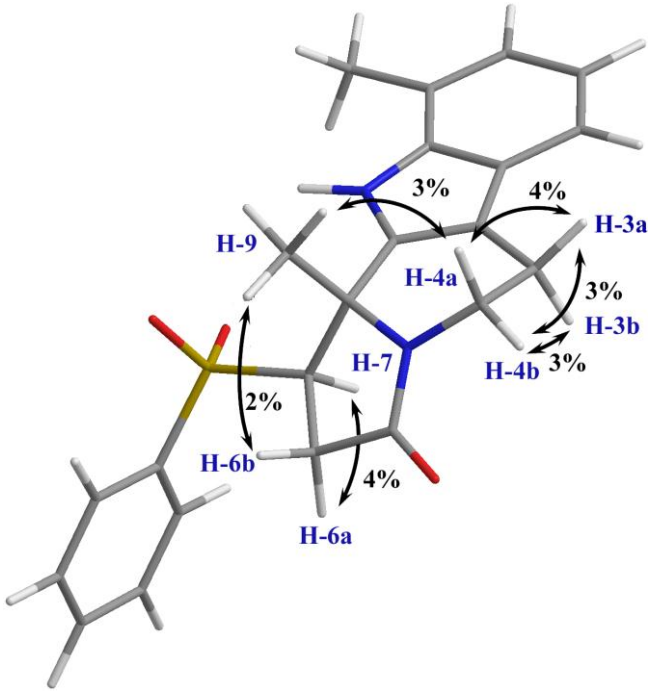
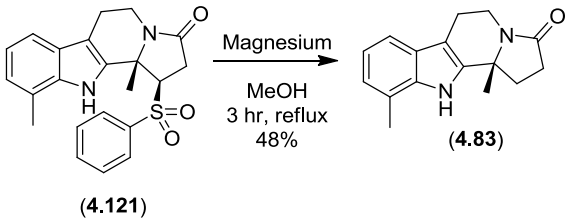


Figure 4.3: Results of NOE experiments on phenyl sulphone (**4.121**)

In order to prove the absolute stereochemistry of phenyl sulphone (**4.121**), the phenyl sulfone moiety was removed in the presence of magnesium to afford the corresponding product (**4.83**) in 48% yield (Scheme 4.26). The optical rotation of product (**4.83**) ($[\alpha]_D^{21}$ = + 176.7 (c = 1.25 in $CHCl_3$), 72% ee) was found to be positive and comparable in magnitude to the optical rotation of cyclised product (**4.83**) (($[\alpha]_D^{21}$ = +215.6 (c = 1.25 in $CHCl_3$), 92% ee)) synthesised by Michael Muratore (Scheme 4.19).



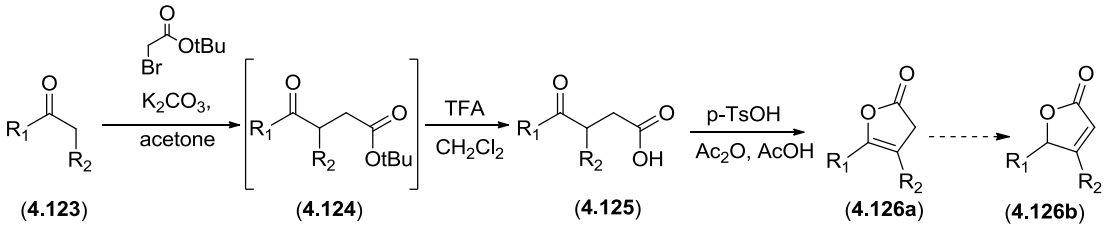
Scheme 4.26: Removal of the phenyl sulphone moiety

An impressive collection of cyclised products (**4.114**) as single diastereomers, were obtained from the Pictet-Spengler cyclisation of aminols (**4.113**) in the presence of a BINOL-derived phosphoric acid catalyst. However, a more direct, higher yielding route to Pictet-Spengler products (**4.114**) was investigated, beginning with the construction of enol lactones.[85]

4.3.3 Extension of the methodology to the use of enol lactones

Enol lactones were prepared for those compounds which gave the highest ees in the Pictet-Spengler reaction of aminols (**4.113**) (Table 4.6). Firstly in the synthesis of enol lactones (**4.126a**),

oxoesters (**4.124**) were prepared from the alkylation of alkyl ketones (**4.123**) with *tert*-butyl bromoacetate under basic conditions. The crude reaction mixtures were hydrolysed with trifluoro acetic acid and purified to yield oxoacids (**4.125**). Oxoacids (**4.125**) proved to be unstable to silica so were afforded in relatively low yields after purification. Phenyl sulphone oxoester (**4.130**) was isolated prior to ester hydrolysis. Exposure of oxoester (**4.130**) to TFA furnished the oxoacid, which due to its instability on silica was not isolated but used crude in the lactonisation reaction. With the exception of methyl ester enol lactone (**4.131**), the enol lactones were obtained in poor yield due to the tautomerisation of the double bond to form α,β-unsaturated lactone (**4.126b**). It was necessary to monitor the reaction to form enol lactones (**4.126a**) very carefully as α,β-unsaturated lactone (**4.126b**) proved to be the thermodynamic product of the reaction and the desired enol lactone would not be isolated if the reaction was left for too long. When crude phenyl sulphone oxoacid was heated to 60 ºC for two hours in the presence of *p*-TsOH, acetic anhydride and acetic acid, enol lactone (**4.134**) was isolated in a poor 15% yield. Decreased reaction times and reaction temperatures failed to improve the yield of enol lactone (**4.134**), which was only ever obtained in a 12-15% yield.



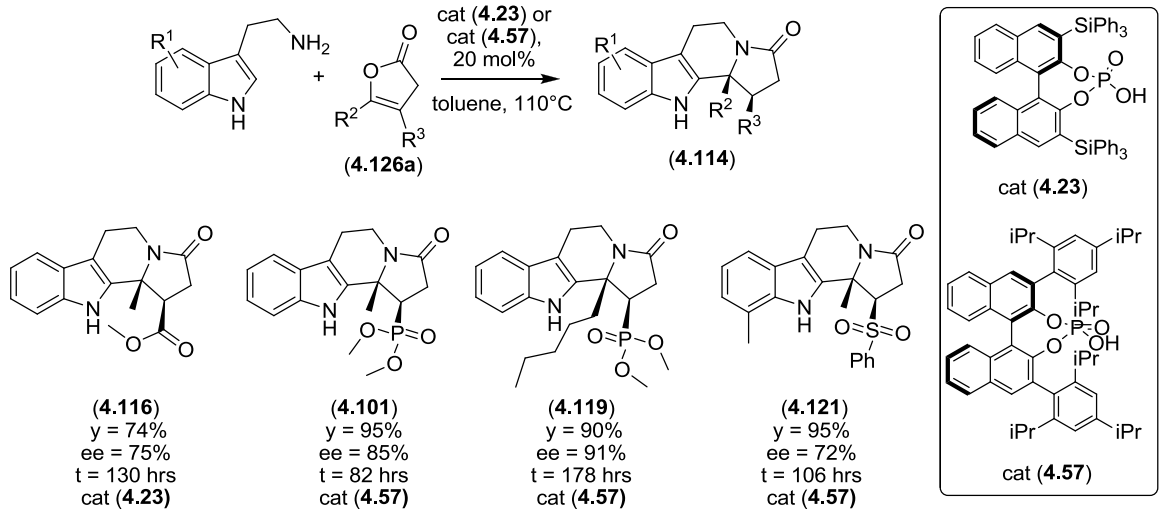
Entry	Enol lactone	R_1	R_2	Yield of oxoacid (**4.125**)	Yield of enol lactone (**4.126a**)
1	(**4.131**)	Me	CO_2Me	40%	74%
2	(**4.132**)	Me	$P(O)(OMe)_2$	46%	64%
3	(**4.133**)	n-pentyl	$P(O)(OMe)_2$	65%	41%
4	(**4.134**)	Me	SO_2Ph	57%*	15%$^{\Psi}$

* Yield of isolated *t*-butyl oxoester. $^{\Psi}$ Yield of enol lactone from *t*-butyl oxoester.

Table 4.6: Yields of oxoacids (**4.125**) and enol lactones (**4.126a**)

With enol latones (**4.126a**) in hand, Pictet-Spengler reactions with tryptamine or 7-methyl tryptamine in the presence of a BINOL-derived phosphoric acid derived catalyst were conducted using optimal reaction conditions[78] (Scheme 4.27). Reaction yields were slightly improved by using enol lactones in the Pictet-Spengler reaction rather than aminols but enantioselectivities remained the same with the exception of methyl ester (**4.116**) where the ee decreased from 92% to 72%. Reaction times were at least doubled by using enol lactones (**4.126a**) in an intermolecular reaction rather than aminols (**4.113**) in an intramolecular reaction even when catalyst loadings were increased to 20%. This was to be expected due to the reaction rate of intermolecular reactions compared with intramolecular reactions especially at high dilution (4.8 mM).

At this point, it was decided that an investigation into the mechanistic pathway of the reaction by identifying key reaction intermediates would be useful to gain an insight into the strong preference for *syn* cyclised products.

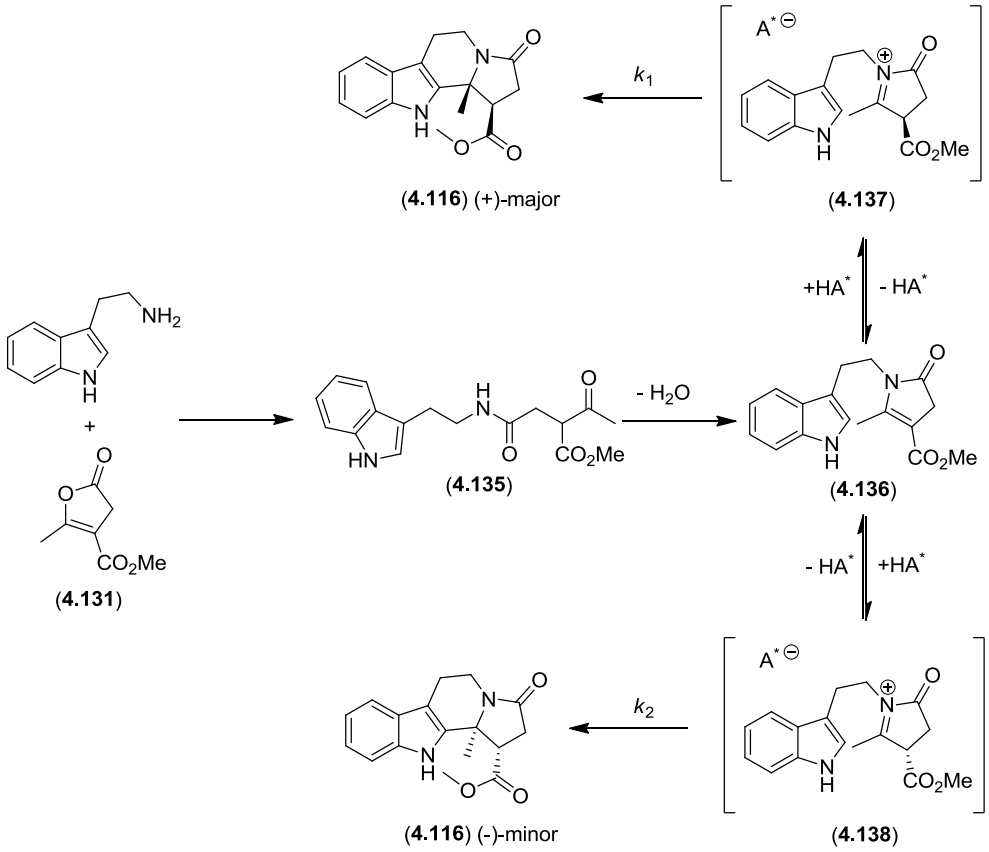


Scheme 4.27: The employment of enol lactones (**4.126a**)

4.3.4 Mechanistic studies

When following the progress of a Pictet-Spengler cyclisation of an enol lactone and tryptamine in the presence of a chiral phosphoric acid catalyst, two different intermediates could be seen by TLC. The first intermediate to appear had a lower R_f value than the product, and the second had a very similar R_f value to the product. In an attempt to isolate the first intermediate a cyclisation reaction of enol lactone (**4.131**) with tryptamine was conducted under standard reaction conditions but stopped after 10 minutes by cooling to room temperature. The first intermediate was isolated in a 65% yield and was found to be oxoamide (**4.135**) (Scheme 4.28). The reaction was repeated following the same protocol but was allowed to proceed for 50 minutes before being quenched by triethylamine. The second intermediate was isolated in a 43% yield and identified as pro-chiral enamide (**4.136**). In boiling toluene, in the presence of a catalytic amount of *para*-toluenesulfonic acid, enamide (**4.136**) readily cyclised to form a single diastereomer of (±)-(**4.116**). The observation that a single diastereomer of methyl ester (**4.116**) was obtained even under racemic conditions suggested that the preference for the group at the quaternary centre and the group α-to the quaternary centre to be on the same side of the lactam ring was under substrate control rather than catalyst control. The observed enantiocontrol in the reaction was consistent with the rapid and reversible formation of iminium-catalyst complexes (**4.137**) and (**4.138**), and the faster rate of formation of major product (**4.137**) compared to minor product (**4.138**) due to matched substrate and catalyst control. This proposed reaction pathway was consistent with a type I DYKAT (dynamic kinetic asymmetric transformation) mechanism, first introduced by Trost *et al.*[86] DYKAT was defined as: "The de-symmetrization of racemic or diastereomeric mixtures involving interconverting diastereomeric intermediates-implying different equilibrium rates of the stereoisomers".[87] A type I DYKAT mechanism features the interconversion of a chiral catalyst

chelated to an achiral intermediate into two different diastereomeric substrate-catalyst complexes before the formation of two diastereomeric products.



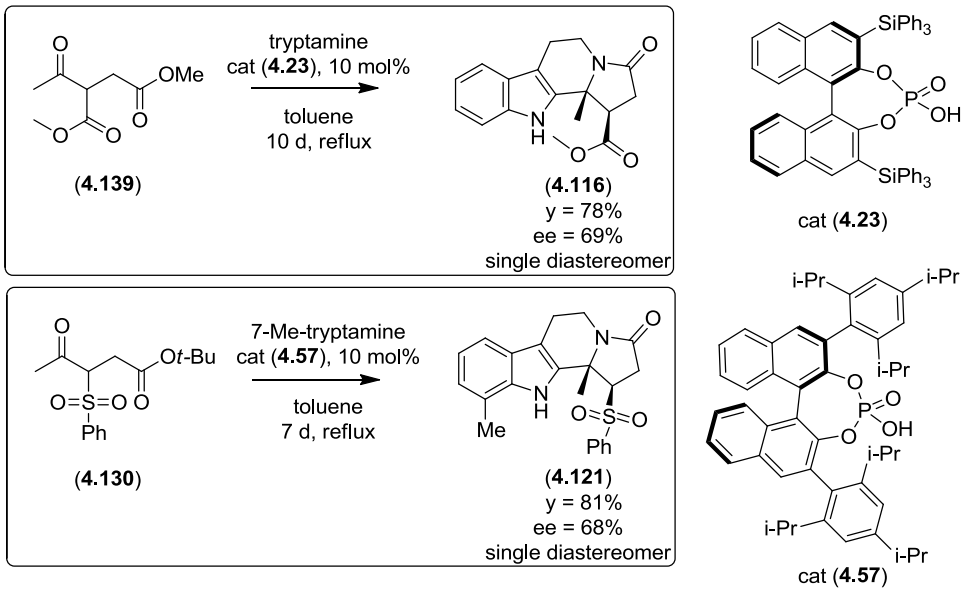
Scheme 4.28: Proposed reaction mechanism

With an insight into the reaction pathway, it was decided that further exploration of the reaction scope was needed. Specifically, to ascertain whether it was necessary for the group adjacent to the quaternary centre to have an electron withdrawing character or whether an alkyl chain at this position would also result in a cyclisation reaction via an enamide intermediate such as (**4.136**). It was also deemed necessary to improve the syntheses of enol lactones (**4.126a**) or to find an alternative starting material which could react with tryptamine and undergo a Pictet-Spengler reaction.

4.3.5 A new approach: The cascade reaction with oxo-acids and esters

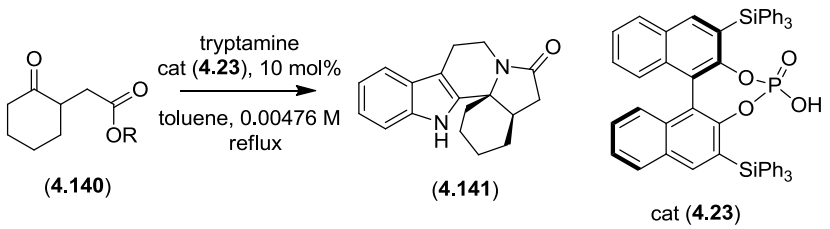
Enol lactones are very reactive species.[88] This was proved by closely monitoring the Pictet-Spengler reaction and observing the disappearance of enol lactone (**4.131**) after 10 minutes of refluxing in toluene with tryptamine and an acid catalyst. During the reaction, tryptamine attacks the enol functionality and causes the lactone ring to be opened to form an oxoamide such as (**4.135**). It was postulated that under the established Pictet-Spengler cyclisation conditions, tryptamine may react with a straight chain ester to give the same intermediate oxoamide, and therefore straight chain esters could be used directly in the Pictet-Spengler reaction with tryptamine.

Reactions employing ester (**4.139**) and phenyl sulphone (**4.130**) as straight chain esters in the Pictet-Spengler reaction with tryptamine were conducted and found to yield cyclised products (**4.116**) and (**4.121**) respectively (Scheme 4.29). The reaction times were considerably longer and starting materials were still observed by TLC after days of refluxing in toluene, however reaction yields remained high and were comparable with those previously obtained. The enantiomeric excess only decreased slightly for Pictet-Spengler products (**4.116**) and (**4.121**) compared to those obtained when enol lactones were employed as starting materials. However, this presented an attractive method to access Pictet-Spengler products as it avoided the preparation of enol lactones which could only be synthesised in low yields.



Scheme 4.29: Formation of Pictet-Spengler products (**4.116**) and (**4.121**) from esters (**4.139**) and (**4.130**) respectively

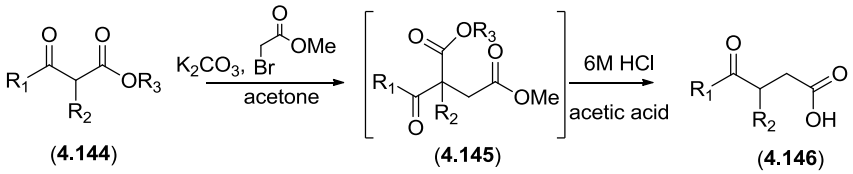
With the development of an attractive method for the formation of Pictet-Spengler products, an investigation into the reaction scope employing the new methodology began. Various electron withdrawing groups were tried as the group adjacent to the quaternary centre but alkyl chains and rings had not been employed. To address this, a preliminary study was conducted using commercially available ethyl 2-(2-oxocyclohexyl)acetate (Table 4.7, entry 1). Pleasingly after 24 hours of refluxing in toluene in the presence of triphenyl silyl phosphoric acid catalyst (**4.23**) the Pictet-Spengler product was isolated in a 77% yield, in 82% ee and in >98:2 dr. Encouraged by these results, the dependence of the reaction time and ee on leaving group R was investigated. The methyl ester and carboxylic acid derivative of (**4.140**) were prepared and used in the Pictet-Spengler cyclisation with tryptamine. Interestingly there was not a large difference in the ee's or dr's obtained, and it was concluded that carboxylic acids and different esters could be used in the reaction without influencing the reaction time or the ee and yield of the final Pictet-Spengler product.



Entry	R	Time/hrs	Yield	dr	ee
1	Et	24	77%	>98:2	82
2	Me	24	80%	>98:2	83
3	H	24	77%	>98:2	81

Table 4.7: A screen of starting materials used to access Pictet-Spengler adduct (**4.141**)

With these pleasing results in hand, the reaction scope was explored by first synthesising a selection of carboxylic acids bearing alkyl chains and rings (Table 4.8). Carboxylic acids (**4.146**) were prepared by the alkylation of 1,3-dicarbonyls (**4.144**) with methyl bromoacetate followed by Krapcho decarboxylation and concomitant hydrolysis of the terminal ester in the presence of 6M HCl and acetic acid. They were obtained in moderate yields and it was possible to prepare them on a multigram scale.

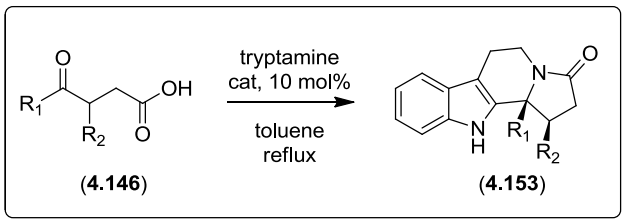


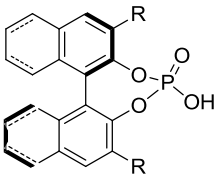
Entry	Compound no.	R_1	R_2	R_3	Yield of (**4.146**)
1	(**4.147**)[89]	Me	Me	Et	37%
2	(**4.148**)	Me	Et	Me	52%
3	(**4.149**)	Me	Bu	Et	47%
4	(**4.150**)[90]	Me	Bn	Et	23%
5	(**4.151**)[91]	$-CH_2CH_2-$	$-CH_2-$	Et	49%
6	(**4.152**)	$-CH_2CH_2CH_2-$	$-CH_2CH_2-$	Me	57%

Table 4.8: Preparation of oxoacids (**4.146**)

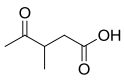
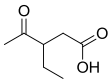
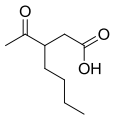
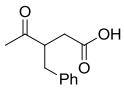
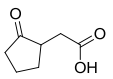
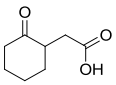
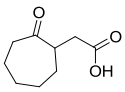
Oxoacids (**4.146**) were screened against a range of phosphoric catalysts in the hope of obtaining Pictet-Spengler adducts (**4.153**) in high yield and in high enantioselectivity and diastereoselectivity (Table 4.9). It became apparent that the employment of different catalysts caused a large variation in enantiomeric excess for a particular substrate. Generally, those catalysts which possessed large bulky R groups such as triphenyl silyl catalysts (**4.23**) and (**4.102**) and triisopropyl phenyl catalyst (**4.57**) afforded Pictet-Spengler products in greater ee. An overall decrease in ee was observed as the length of the alkyl chain at position R_2 increased from 1 to 2 to 4 carbons which suggested that a bulkier group at R_2 interacted less favourably with the catalyst. This observation was confirmed when a bulky benzyl group was introduced at R_2 and consistently gave poor ee's when a range of catalysts were screened. Interestingly the use of oxoacids (**4.151**), (**4.143**) and (**4.152**) with different sized rings afforded Pictet-Spengler products in high ee's when matched with the best

catalysts. In general it was found that the larger the ring size the higher the ee obtained which could be explained by the higher degree of conformational flexibility associated with larger rings which would enable the substrate to orient the ring in such a way as to form a favourable catalyst-substrate interaction.





cat (**4.23**): R = $SiPh_3$
cat (**4.60**): R = 3,5-$(CF_3)_2C_6H_3$
cat (**4.57**): R = 2,4,6-$(^iPr)_3C_6H_2$
cat (**4.39**): R = 9-anthryl
cat (**4.18**): R = 9-phenanthryl
cat (**4.6**): R = 4-$NO_2C_6H_4$
cat (**4.161**): R = $SiMe_3$
cat (**4.102**): R = H_8BINOL $SiPh_3$

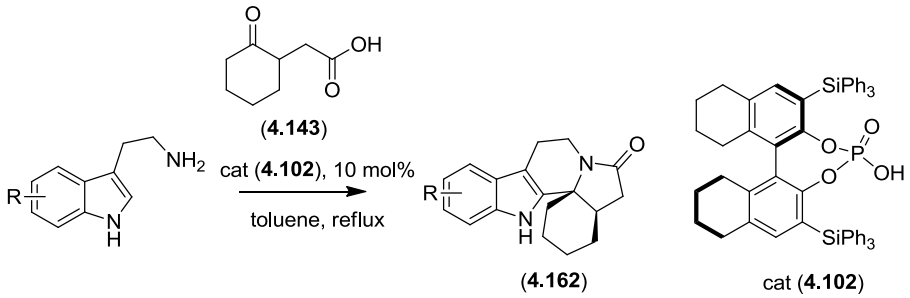
Product no.	(**4.154**)	(**4.155**)	(**4.156**)	(**4.157**)	(**4.158**)	(**4.141**)	(**4.159**)
Acid / Cat							
(**4.23**)	y = 99% ee = 76%	y = 42% ee = 44%	y = 47% ee = 54%	y = 99% ee = 8%	y = 54% ee = 60%	y = 77% ee = 81%	y = 83% ee = 73%
(**4.60**)	y = 51% ee = 61%		y = 69% ee = 38%	No reaction	y = 57% ee = 68%	y = 95% ee = 63%	y = 72% ee = 74%
(**4.57**)	y = quant ee = 14%		y = 70% ee = 50%	y = 46% ee = 32%	y = 53% ee = 18%	y = 87% ee = 14%	
(**4.39**)	y = 80% ee = 2%		y = 98% ee = 40%	y = 54% ee = 21%	y = 32% ee = 8%	y = 95% ee = 43%	
(**4.18**)	y = 79% ee = 14%		y = 82% ee = 32%	y = 82% ee = 9%	y = 66% ee = 25%	y = quant ee = 53%	
(**4.6**)	y = 93% ee = 30%		y = 75% ee = 7%	y = 75% ee = 7%	y = 26% ee = 50%	y = 86% ee = 57%	
(**4.161**)	y = quant ee = 43%		y = 55% ee = 43%	y = 62% ee = 27%	y = 90% ee = 35%	y = 89% ee = 74%	
(**4.102**)	y = 55% ee = 74%	y = 34% ee = 61%	y = quant ee = 59%	y = quant ee = 12%	y = 76% ee = 22%	y = 63% ee = 82%	y = 90% ee = 86%

N.B. A blank box in the table indicates that a reaction has not been conducted

Table 4.9: Screening different catalysts with different carboxylic acids

With the results of the catalyst screen in hand and an optimised ee for each Pictet-Spengler adduct, attention was turned to using variously substituted tryptamines and observing the effect on enantiomeric excess. As seen previously in the preliminary work on phosphoric acid catalysed Pictet-Spengler reactions by Michael Muratore, the presence of a halogen at position 4 or 5 in the indole ring increased the ee by 3-7% typically.[78] When 7-methyl tryptamine was employed in the reaction the ee rose by 12% in two cases (Scheme 4.19). In view of these findings, 5-bromo tryptamine, 7-methyl tryptamine and 5-methoxy tryptamine were screened with cyclohexanone

oxoacid (**4.143**) (Table 4.10). As expected, the presence of a bromine atom at position 5 on the indole ring (entry 3) gave an increase in ee of 5% when compared with the non-substituted analogue (entry 1). The 7-methyl tryptamine (entry 4) gave an excellent ee of 98%, which amounted to a 15% increase compared to the non-substituted analogue, inline with Michael Muratore's findings. Surprisingly, the presence of the mesomerically donating methoxy substituent on the indole ring (entry 2) caused a slight decrease in enantiomeric excess when compared to the non-substituted derivative. In order to increase the enantiomeric excesses of the Pictet-Spengler products obtained using different oxoacids, 7-methyl tryptamine was used in place of tryptamine as from the substituted tryptamines tried, it had caused the greatest increase in ee.



Entry	Compound no.	R	Time/days	Yield	dr	ee
1	(**4.141**)	H	1	63%	>98:2	83%
2	(**4.163**)	5-OMe	1	90%	>98:2	79%
3	(**4.164**)	5-Br	2	88%	>98:2	88%
4	(**4.165**)	7-Me	2	89%	>98:2	98%

Table 4.10: Investigating the use of differently substituted tryptamines

The absolute and relative stereochemistry of 5-bromo cyclised adduct (**4.163**) was confirmed by single crystal X-ray crystallography. The configuration (4a*R*,14b*R*) was in agreement with the previously observed stereochemistry when the (*R*) enantiomer of the catalyst was used to induce enantioselectivity. The relative stereochemistry was confirmed to be *syn*, agreeing with the relative stereochemistry observed for β-carbolines bearing an electron-withdrawing group adjacent to the quaternary stereogenic centre (Figure 4.4).

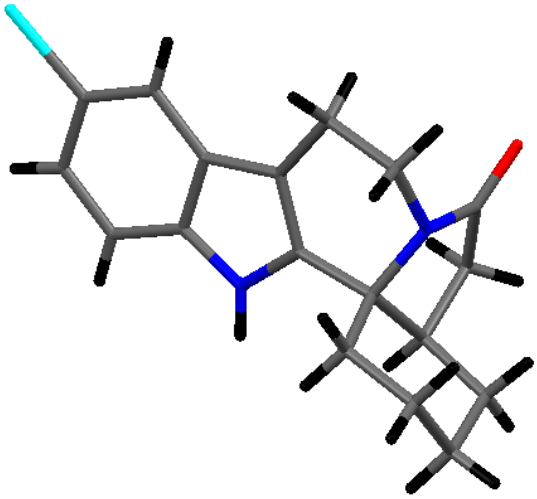
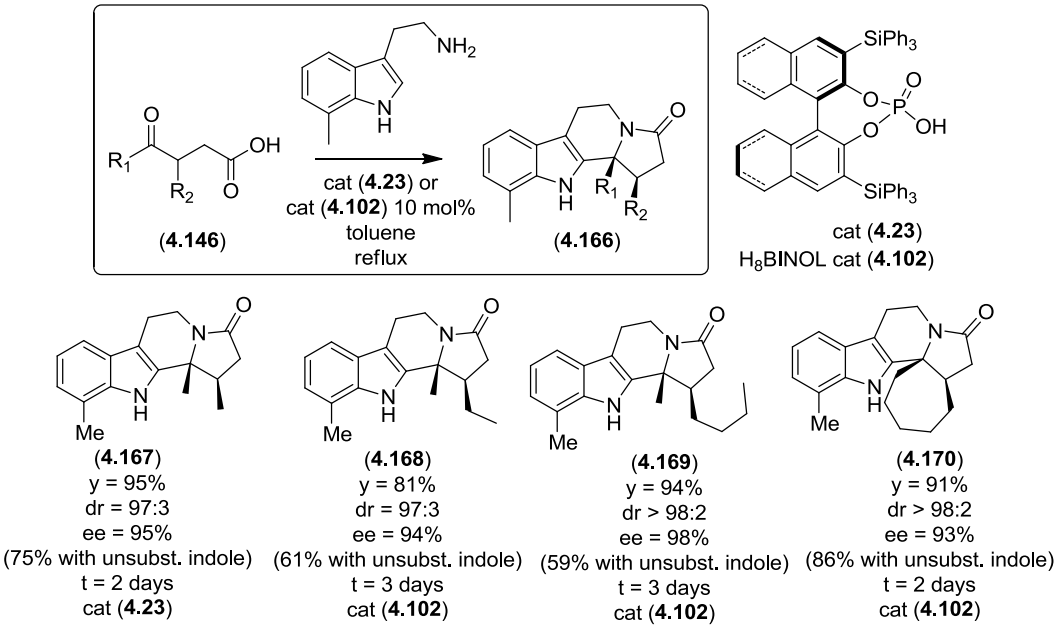


Figure 4.4: Single crystal X-ray structure of 5-bromo adduct (**4.164**)

The results of the reaction of 7-methyl tryptamine with four different oxoacids are summarised below (Scheme 4.30). For those oxoacids which gave moderate enantioselectivities when reacted with tryptamine to give cyclised products (**4.155**) and (**4.156**), a large increase in ee (33% and 39% respectively) was found when 7-methyl tryptamine was used instead. For those oxoacids which had given good ee's when reacted with tryptamine, the employment of 7-methyl tryptamine gave ee's in excess of 90% (Pictet-Spengler products (**4.167**) and (**4.170**)).



Scheme 4.30: Exploring the scope using 7-Me tryptamine

The relative stereochemistry of 7-methyl tryptamine adduct (**4.167**) was determined by single X-ray crystallography, and as expected the adjacent stereocentres on the lactam ring were found to occupy a *syn* arrangement (Figure 4.5).

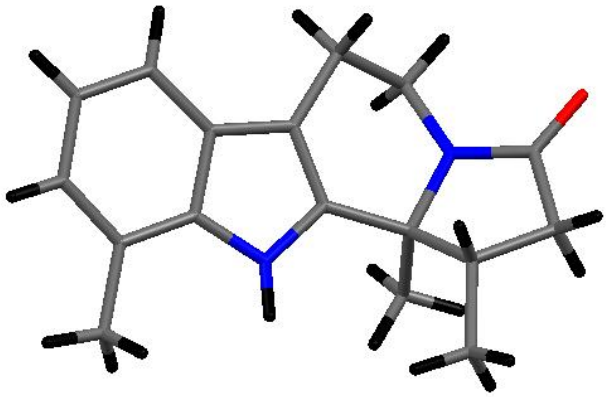
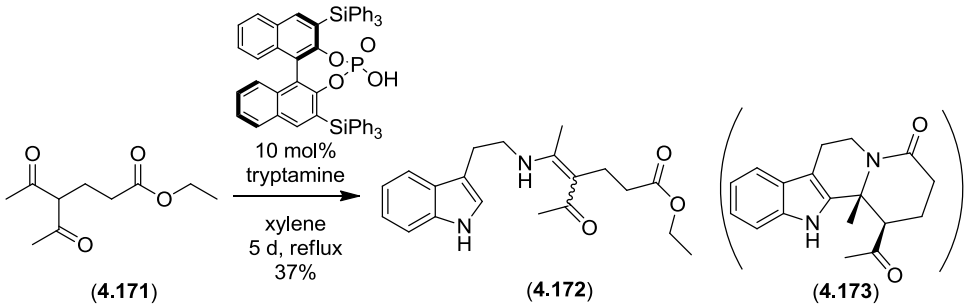


Figure 4.5: Single X-ray crystal structure of 7-methyl tryptamine adduct (**4.167**)[Ψ]

[Ψ] Crystal grown by Michael Muratore

In a final attempt to increase the scope of the methodology a reaction with commercially available ethyl 4-acetyl-5-oxohexanoate and tryptamine was tried under standard cyclisation conditions (10 mol% catalyst in toluene at reflux). It was hoped that by employing ethyl ester (**4.171**) in the reaction δ-lactam (**4.173**) would be dominant reaction product. However standard reaction conditions failed to promote any reaction so harsher conditions were tried. The solution was refluxed for 5 days in xylene, after which a polar product appeared by TLC analysis. Amine (**4.172**) was isolated in a 37% yield which led to the conclusion that the formation of a δ-lactam bearing an electron withdrawing group was unflavoured (Scheme 4.31).



Scheme 4.31: Attempt at forming δ-lactam (**4.173**)

4.4 Summary

A series of BINOL-derived phosphoric acid catalysed cascades have been developed, all featuring an asymmetric Pictet-Spengler reaction. Through careful optimisation and planning, each methodology has been improved upon to provide subsequent methodologies leading to more complex products with greater enantioselectivities, and the use of structurally simpler starting materials to achieve this. Furthermore, an investigation into the reaction mechanism by which these products are constructed has been conducted and has revealed the set of intermediates formed and has provided a rationale for the impressive diastereoselectivity observed. NOE

experiments and x-ray crystallography have proved the relative and absolute stereochemistry of the Pictet-Spengler cyclisation products respectively. Details of how these methodologies were applied in the studies towards the synthesis of subincanadine B are discussed in the following chapter.

Chapter 5: Synthetic studies towards Subincanadine B – asymmetric Pictet-Spengler cyclisation approach

5.1 Concept and Aims

After the successful development of a versatile, reliable methodology employing BINOL-derived phosphoric acid catalysts, the task which remained was the application of the methodology to the synthesis of subincanadine B.

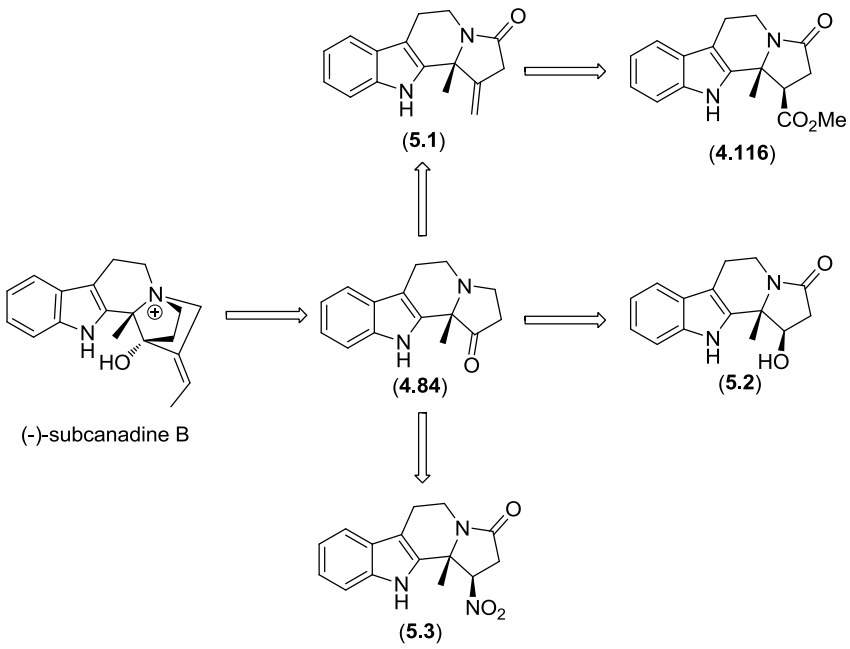
Specifically the aims of this study were:

1) To synthesise a series of substrates which could be used in the Pictet-Spengler reaction and provide products from which subincanadine B could be accessed.
2) With the chosen intermediate, explore possible synthetic transformations towards the synthesis of subincanadine B.

5.2 Results and Discussion

5.2.1 Studies towards the synthesis of ketone (**4.84**)

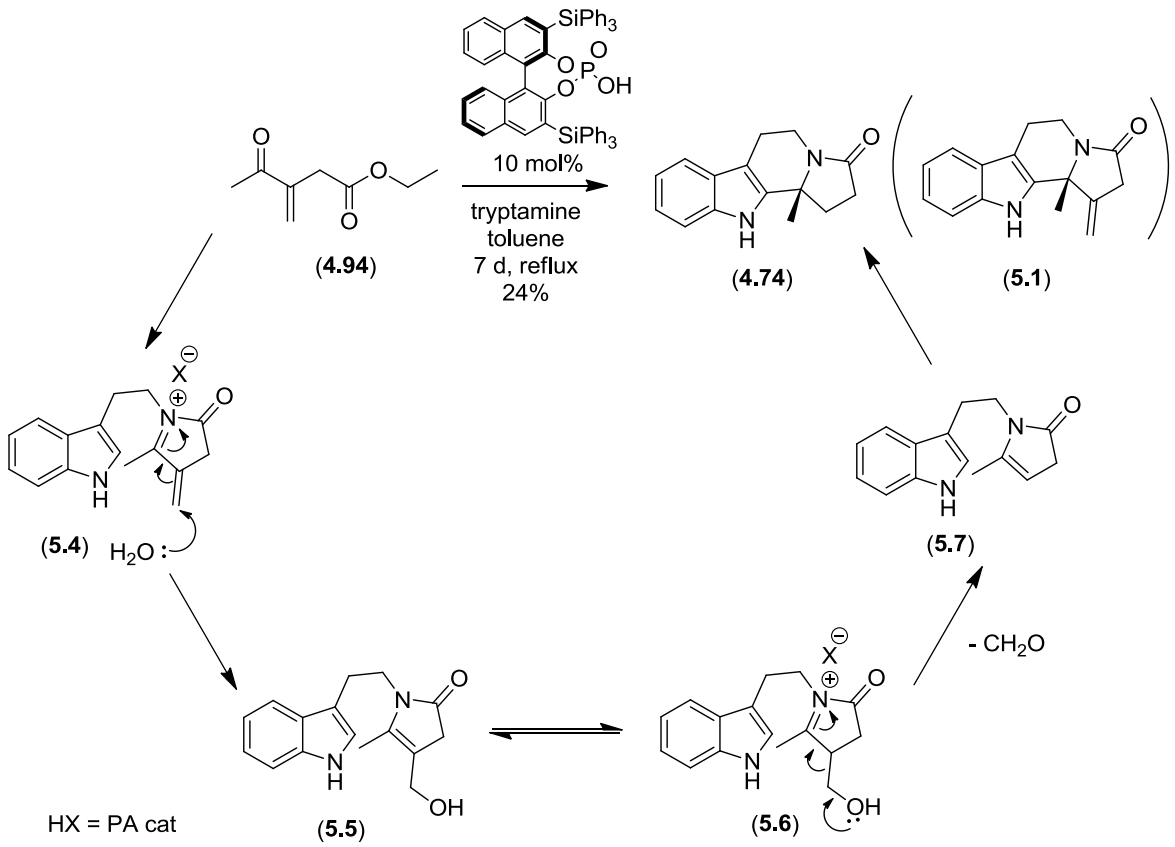
In order to access subincanadine B using the methodology developed in chapter 4, it was necessary to first obtain ketone (**4.84**) (Scheme 5.1). This could be achieved by the synthesis of alkene (**5.1**) followed by amide reduction and subsequent dihydroxylation of the alkene and oxidative cleavage.[54] A more direct approach to ketone (**4.84**) would be to synthesise β-hydroxy amide (**5.2**) followed by amide reduction and oxidation of the secondary hydroxyl group to a ketone. An alternative method to access ketone (**4.84**) would be to synthesise β-nitro amide (**5.3**, reduce the amide and convert the nitro group to a ketone via a Nef reaction.[92] If these synthetic routes to access ketone (**4.84**) failed then methyl ester (**4.116**) which had been synthesised in 78% yield with an ee of 72% could be manipulated to access ketone (**4.84**), via reduction of the ester and amide functionalities to give a primary alcohol. This could be eliminated to give terminal alkene (**5.1**) which could undergo dihydroxylation and oxidative cleavage to yield the desired ketone (**4.84**).



Scheme 5.1: Retrosynthetic analysis of ketone (**4.84**)

5.2.1.1 Attempts to form alkene (**5.1**)

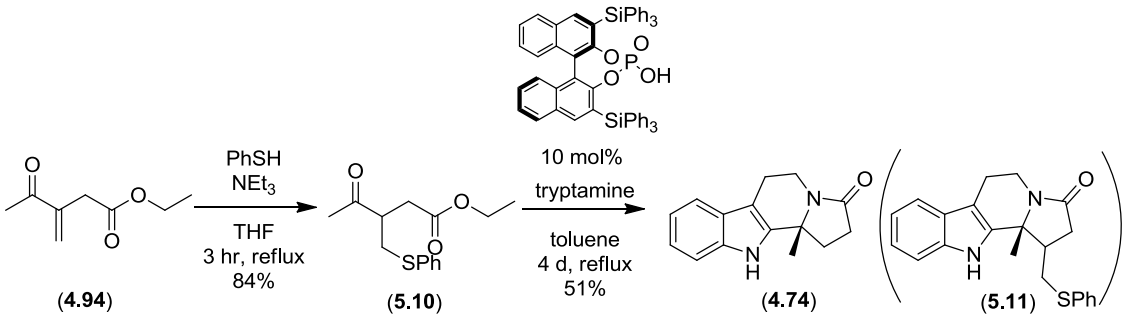
α,β-Unsaturated ketone (**4.94**) had been synthesised previously as mentioned in chapter 4 (Scheme 4.23). It had been reacted with tryptamine in the presence of Lewis acid $AlMe_3$ and the amine had undergone a Michael addition with the alkene to form an undesired product. It was hoped that using a milder acid catalyst, a Pictet-Spengler reaction would occur instead. However, under standard Pictet-Spengler cyclisation conditions product (**4.74**) was obtained unexpectedly in a 24% yield (Scheme 5.2). A rationale for the formation of product (**4.74**), which was previously synthesised by Jacobsen *et al.*,[75] is outlined below.



Scheme 5.2: Proposed rationale for the formation of unexpected product (**4.74**)

Following the formation of iminium ion (**5.4**), the addition of water to the terminal alkene was thought to occur and give rise to enamide (**5.5**) which would equilibrate in solution to iminium ion (**5.6**). Formaldehyde would be eliminated and enamide (**5.7**) would be the resulting product which could subsequently undergo a Pictet-Spengler cyclisation to yield adduct (**4.74**).

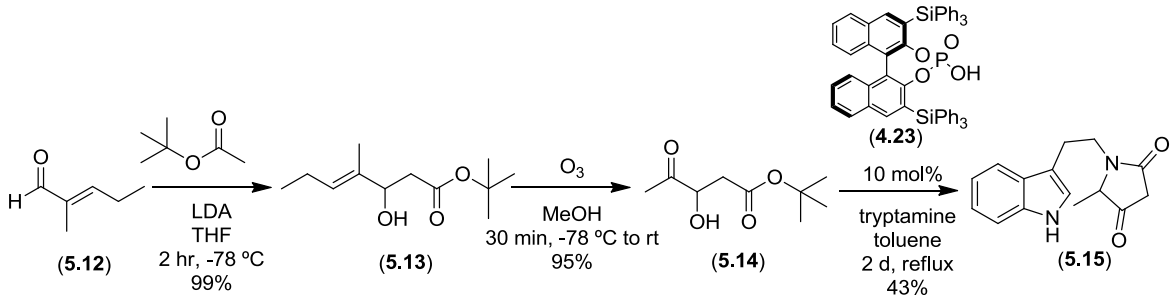
In an attempt to avoid the formation of cyclic adduct (**4.74**), the terminal alkene was protected as a phenyl sulfane to prevent the addition of water[93] (Scheme 5.3). Unfortunately when this was subjected to Pictet-Spengler cyclisation conditions in the presence of a phosphoric acid catalyst, undesired product (**4.74**) was isolated in a 51% yield. No further attempts to avoid water addition and prevent elimination were made, and attention was turned to the preparation and use of β-hydroxyester (**5.14**) to access β-oxyamide (**5.2**).



Scheme 5.3: Pictet-Spengler reaction with thiol (**5.10**)

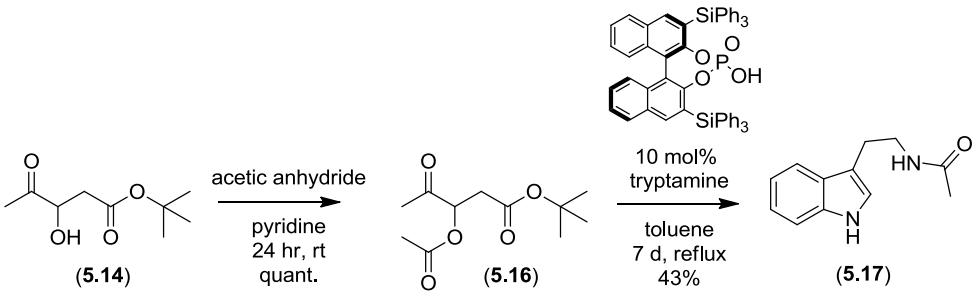
5.2.1.2 Attempts to form β-oxyamide (**5.2**)

β-Oxyester (**5.14**) was prepared in two facile steps from commercially available (*E*)-2-methylpent-2-enal in an overall yield of 94%[94] (Scheme 5.4). When subjected to Pictet-Spengler cyclisation conditions in the presence of phosphoric acid catalyst (**4.23**), pyrrolidine dione (**5.15**) was isolated in 43% yield. Presumably, once the enamide intermediate had formed, tautomerisation had occurred to form pyrrolidine dione (**5.15**), the thermodynamic product of the reaction.



Scheme 5.4: Pictet-Spengler reaction of β-hydroxy ester (**5.14**)

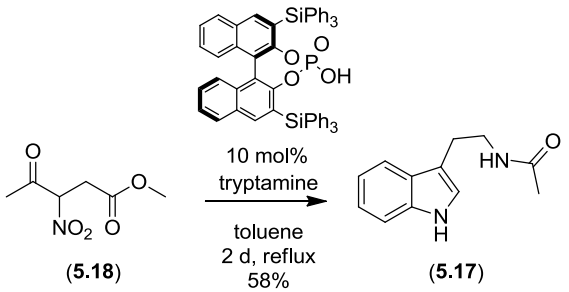
In an attempt to suppress the formation of pyrrolidine dione (**5.15**), the hydroxyl group of β-oxyester (**5.14**) was protected as an acetyl (Scheme 5.5). This would prevent tautomerisation occurring and by using a small protecting group it was hoped that the enantiomeric excess of the desired cyclised product would be high. However, under Pictet-Spengler cyclisation conditions, tryptamine underwent a nucleophilic addition reaction with the acetyl protecting group on the ester rather than reacting with the ketone and *tert*-butyl-ester functionalities. Amide (**5.17**)[95] was isolated in a 43% yield, and there was no trace of the Pictet-Spengler product by ^{1}H NMR or TLC analysis.



Scheme 5.5: Reaction of acetate (**5.16**) with tryptamine under Pictet-Spengler cyclisation conditions

5.2.1.3 Attempts to form β-nitroamide (**5.3**)

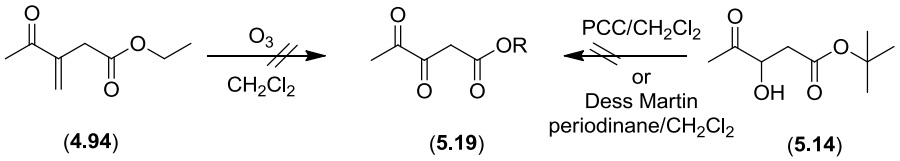
An alternative approach to desired ketone (**4.84**) was explored involving the use of β-nitroester (**5.18**). This was prepared in the group and was used in the Pictet-Spengler reaction with tryptamine in the presence of a phosphoric acid catalyst (Scheme 5.6). Unfortunately, the β-nitroester moiety proved to be a good leaving group when the adjacent ketone was attacked by tryptamine. The result was the formation of previously isolated amide (**5.17**) in 58% yield after two days at reflux.



Scheme 5.6: Reaction of β-nitroester (**5.18**) with tryptamine under Pictet-Spengler cyclisation conditions

5.2.1.4 Attempts to access β-ketoester (**5.19**) directly

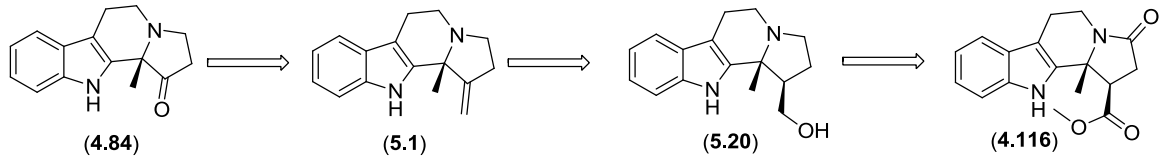
After the disappointing results obtained in the attempts to synthesise ketone (**4.84**), a more direct approach was tried involving the preparation of β-ketoester (**5.19**) (Scheme 5.7). Firstly ozonolysis of α,β-unsaturated ketone (**4.94**) was attempted but only starting material was recovered. Secondly, oxidation of β-hydroxy ester (**5.14**) was tried using Jones reagent but resulted in a complex mixture of products. Oxidation with Dess Martin periodinane[96] also produced a variety of unstable products as seen in the ^{1}H NMR. Further attempts to synthesise β-ketoester (**5.19**) were abandoned and attention was turned finally to the manipulation of methyl ester (**4.116**) into ketone (**4.84**).



Scheme 5.7: Attempts at formation of β-ketoester (**5.19**)

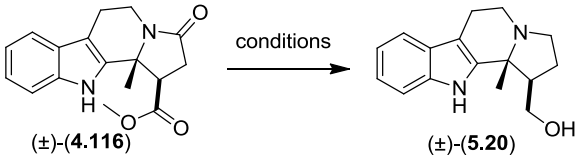
5.2.2 Synthetic studies towards subincanadine B via methyl ester (**4.116**)

Methyl ester (**4.116**) had previously been synthesised in good yield and enantiomeric excess and it was thought that modification to desired ketone (**4.84**) could be achieved by three transformations (Scheme 5.8). Firstly, the amide and ester functionalities could be simultaneously reduced to give alcohol (**5.20**), secondly, the primary alcohol could be eliminated to provide alkene (**5.1**), which could undergo dihydroxylation and oxidative cleavage in the final transformation to yield ketone (**4.84**).



Scheme 5.8: Retrosynthetic analysis of ketone (**4.84**) from methyl ester (**4.116**)

A variety of reducing agents were screened including a borane-tetrahydofuran complex, a borane-dimethylsulfide complex and lithium aluminium hydride[97] (Table 5.1). When a borane-tetrahydrofuran complex was employed in the reaction only the amide was reduced and the methyl ester remained intact. In order to achieve complete reduction of the amide and ester functionalities six equivalents of borane-dimethylsulfide were employed in the reaction (entry 1). Two different reaction products could be seen by TLC after a short reaction time together with starting material. The apolar spot corresponded to the product where the amide had been reduced but the methyl ester was still intact. The more polar product was desired alcohol (±)-(**5.20**), which was isolated in a 34% yield after 24 hours (entry 2). Finally $LiAlH_4$ was employed and alcohol (±)-(**5.20**) was obtained quantitatively.[98, 99]

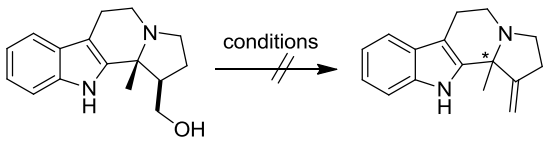


(±)-(**4.116**) (±)-(**5.20**)

Entry	Reagents	Solvent	Temperature	Time/hrs	Yield
1	$BH_3.SMe_2$, 6 eq	THF	reflux	24	34%
2	$LiAlH_4$, 4 eq	THF	rt	7	quant.

Table 5.1: Amide and ester reduction optimisation

With alcohol (±)-(**5.20**) in hand, reagents were screened which had been shown in the literature to assist with the elimination of a primary hydroxyl group to form an alkene (Table 5.2). Firstly, potassium *tert*-butoxide was tried using a procedure by Mazitscheck and Giannis[100] for the elimination of a primary alcohol in their synthesis of ovalicin analogues. However, no alkene signals were observed in the crude ^{1}H NMR so an alternative method of alcohol elimination was tried. DCC/CuCl had been used by Qin *et al.*[101] in the dehydration of a secondary alcohol in the presence of an indole moiety, however under these conditions the ^{1}H NMR spectrum of the crude reaction mixture was complicated and no alkene peaks were visible. In a final attempt to form alkene (±)-(**5.1**), P_2O_5 was employed as a dehydrating agent after demonstrating the ability to effectively eliminate a tertiary alcohol in the synthesis of diketopiperazine (**2.51**) (Scheme 2.14). Unfortunately no product was seen in the crude ^{1}H NMR or in the mass spectrum so this approach was abandoned.

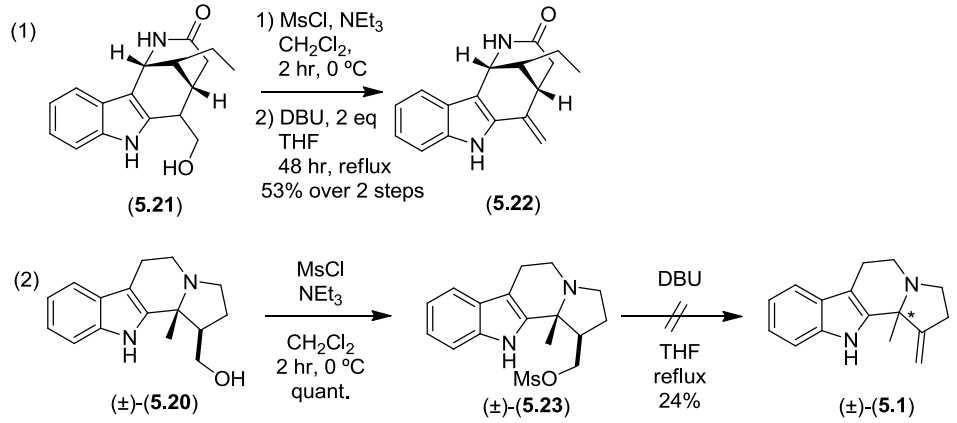


(±)-(**5.20**) (±)-(**5.1**)

Entry	Reagents	Solvent	Temperature	Time/hrs
1	^{t}BuOK, 3 eq	DMF	100 ºC	3
2	DCC, 5eq, CuCl, 10 eq	toluene	reflux	48
3	P_2O_5, 2 eq	toluene	reflux	4

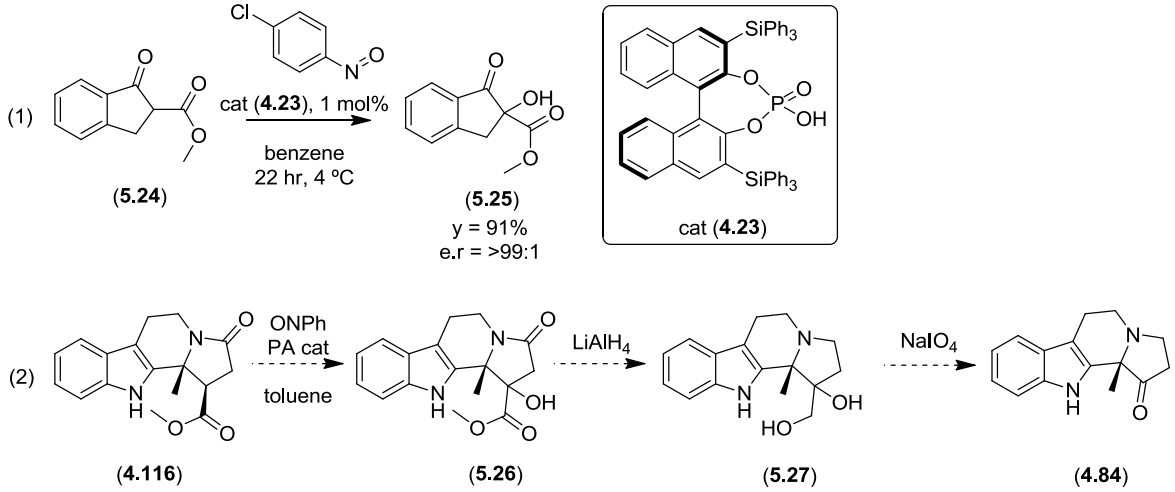
Table 5.2: Conditions tried to form alkene (±)-(**5.1**) from primary alcohol (±)-(**5.20**)

An alternative strategy to eliminate the primary alcohol was to convert it into a good leaving group and then attempt elimination. This was the approach adopted by Amat and Bosch[102] in their syntheses of uleine alkaloids. They firstly mesylated alcohol (**5.21**) and then effected elimination with DBU[103] to furnish desired alkene (**5.22**) in 53% yield over two steps (Scheme 5.9 (1)). The fact that their substrate was structurally similar to alcohol (±)-(**5.20**) suggested that success in the elimination of the primary alcohol could be achieved using their method. Following their procedure, alcohol (±)-(**5.20**) was mesylated quantitatively and then DBU employed to effect elimination (Scheme 5.9 (2)). However although alkene peaks were observed in the crude ^{1}H NMR, isolation of the product was problematic and the reaction did not prove to be easily reproducible.



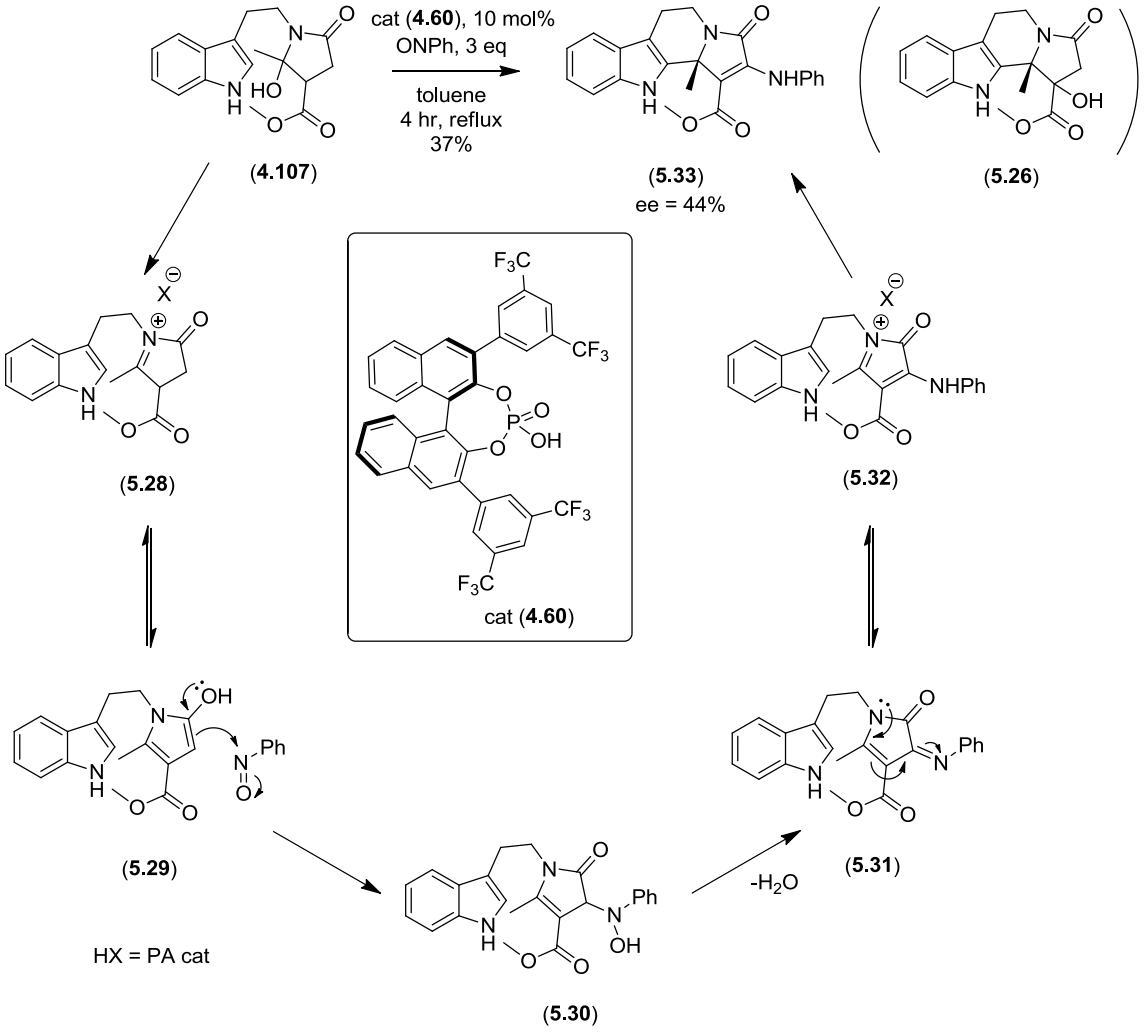
Scheme 5.9: 1) Elimination of a primary hydroxyl group from product (**5.21**) reported by Amat and Bosch. 2) The attempted formation of alkene (±)-(**5.1**) from mesylate (±)-(**5.23**)

An alternative approach to access ketone (**4.84**) via methyl ester (**4.116**) was to first hydroxylate α to the methyl ester functionality with an electrophilic oxygen source. A precedent was found in the literature featuring the α-hydroxylation of β-dicarbonyl compounds with *para*-chloro nitrosobenzene in the presence of a BINOL derived phosphoric acid catalyst[104] (Scheme 5.10 (1)). It was thought that this methodology, developed by Zhong *et al.*, could be used to form desired α-hydroxylated product (**5.26**). Reduction of the ester and amide moieties with lithium aluminium hydride would provide diol (**5.27**) which could be converted to ketone (**4.84**) with sodium periodate (Scheme 5.10 (2)).



Scheme 5.10: 1) α-Hydroxylation of indanone (**5.24**) developed by Zhong *et al.* 2) Synthetic plan to ketone (**4.84**) via α-hydroxylation of the methyl ester

Cyclised methyl ester (±)-(**4.116**) proved to be unreactive when used as the substrate in a reaction with nitrosobenzene in refluxing toluene in the presence of phosphoric acid catalyst (**4.60**). It was suggested that in order for a reaction to take place the reactive enamide would need to be present in solution to react as a nucleophile. In view of this a reaction was tried using aminol (**4.107**) in place of cyclised methyl ester (±)-(**4.116**). Under the previously described conditions, unexpected product (**5.33**) was afforded in a 37% yield and 44% ee. Cyclised product (**5.33**) was found to be the dominant product of the reaction (Scheme 5.11). In order to rationalise the formation of amine (**5.33**), a mechanism was proposed which began with the formation of iminium ion (**5.28**). Tautomerisation to hydroxy pyrrole species (**5.29**) would enable nucleophilic attack by the pyrrole species onto nitrosobenzene to furnish enamide (**5.30**). Loss of water and further tautomerisation would give iminium ion (**5.32**) which could undergo a Pictet-Spengler reaction to afford the observed product.



Scheme 5.11: Reaction of methyl ester aminol (**4.107**) with nitrosobenzene

The observed reactivity showed that the carbon α to the amide on the lactam ring would act as a nucleophile in preference to the carbon α to the methyl ester. Despite the failed attempt to hydroxylate α to the ester, an interesting product had been obtained which could be used in the development of a future methodology.

5.3 Summary

Despite trying different approaches to access ketone (**4.84**), a viable synthesis was not achieved. Further investigation into the application of the methodology developed in chapter 4 to the synthesis of subincanadine B is required. An insight has been gained into the reactivity of methyl ester enamide (**4.136**) in the presence of an electrophilic species and has led to the discovery of a new methodology exploiting the reactivity of the enamide intermediate at the position adjacent to the amide functionality.

Chapter 6: Conclusions and future work

6.1 Conclusions

In conclusion, this thesis describes the development of two methodologies which were both used in the synthetic studies towards subincanadine B. Both methodologies featured the use of a Brønsted acid catalyst in the formation of a chiral quaternary centre in excellent diastereoselectivity and enantiomeric excess.

In the first methodology, the addition of various tryptamine nucleophiles to a proline derived diketopiperazine under Brønsted acidic conditions was developed. The diketopiperazine was found to act as a chiral indicator and induced excellent diastereoselectivity in the products obtained. A range of adducts were afforded bearing different groups at the 3-position of indole (75% average yield over 10 examples). This methodology was used in the synthetic studies towards the synthesis of subincanadine B. The synthesis featured the construction of a fused pentacyclic product (dr = 1.4:1) containing a proline derived diketopiperazine moiety. It was necessary to cleave the diketopiperazine moiety in order to proceed with the synthesis but this did not prove facile and only the least sterically hindered amide bond was susceptible to further reaction. A new methodology to access subincanadine B was investigated.

The new methodology built on the work by Michael Muratore in the enantioselective Pictet-Spengler cyclisation of enol lactones with tryptamine in the presence of a BINOL derived phosphoric acid catalyst. The previous work had focused on obtaining cyclised products in high enantiomeric excesses with different alkyl and aryl groups at the chiral quaternary centre. In this thesis the concept was extended to the formation of Pictet-Spengler products with different groups adjacent to the quaternary stereocentre. The initial methodology explored the intramolecular Pictet-Spengler cyclisation of aminols bearing electron withdrawing groups adjacent to the quaternary stereocentre. Conditions were optimised and eight products were obtained, each bearing a different electron withdrawing group, as single diastereomers in good to excellent enantiomeric excess (64%-91%) and in good yields (64%-94%).

The second development of the methodology was to use substituted enol lactones in an intermolecular Pictet-Spengler reaction with tryptamine which afforded the same Pictet-Spengler products in comparable enantioselectivities and yields.

An investigation into the reaction mechanism of the Pictet-Spengler cyclisation with tryptamine and an enol lactone revealed that a dynamic kinetic equilibrium was operative and that the reaction was proceeding through an achiral enamide intermediate. The observed enantiocontrol in the reaction was consistent with the rapid and reversible formation of two acyl iminium-catalyst complexes, and the faster rate of formation of one of these complexes compared to the other due to matched substrate and catalyst control.

In the final development of the methodology, alkyl groups were introduced adjacent to the quaternary stereocentre and different sized carbon rings were fused to the lactam ring linking the quaternary stereocentre and the adjacent tertiary centre. Instead of employing enol lactones, straight chain esters and carboxylic acids were reacted directly with differently substituted tryptamines. A series of Pictet-Spengler products were afforded in excellent diastereoselectivities, enantioselectivities and yields.

The enantioselective Pictet-Spengler methodology was applied in the synthetic studies towards subincanadine B and although some progress was made, further work is needed to complete the synthesis.

6.2 Future work

Further investigation into the application of the Pictet-Spengler cyclisation cascade to the synthesis of subincanadine B is needed. Initial studies outlined in chapter 5 have shown the difficulties in introducing a methylene unit adjacent to the quaternary stereocentre, but there are other methods which have not been explored and in which an investigation could prove worthwhile. For example, alternative procedures for inserting a hydroxyl group α-to a methyl ester exist in the literature and could be tried.[105,106,107]

The scope of the enantioselective Pictet-Spengler methodology could be broadened by the use of other heterocycles in place of indole to affect cyclisation. Pyrrole,[108] furan or thiophene could be employed in the reaction to generate a wide range of Pictet-Spengler products.

A new methodology could be explored and developed from the new reactivity displayed by the enamide intermediate in the presence of an electrophilic species as detailed in chapter 5. Optimisation of the reaction conditions would be needed before trying reactions with a range of small electrophiles.

Chapter 7: Experimental

7.1 General Procedures

All reactions were performed under an atmosphere of dry nitrogen unless otherwise stated. All glass apparatus was oven dried and cooled under vacuum. For water or O_2 sensitive reactions, glassware was dried again before use by a hot air gun and cooled under a nitrogen atmosphere.

1) Solvents and Reagents

Solvents were removed *in vacuo* using a Büchi rotary evaporator attached to a pump at 40 ºC. Reagents were obtained from commercial suppliers or redistilled if required. Petroleum ether refers to distilled light petroleum of fraction 40-60 ºC. Anhydrous dichloromethane and toluene were purified by distillation from calcium hydride. Anhydrous tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone. Sodium hydride was obtained as a 60% dispersion in mineral oil and was washed with petrol (40-60) followed by drying *in vacuo* prior to use.

2) Chromatography

In all cases of chromatography, distilled solvents were used as eluents. Flash column chromatography was performed using Merck Kiesegal 60 silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Kiesegal 60 F_{254} (230-400 mesh) fluorescent treated silica; the plates were visualised by UV irradiation (254 nm) and stained with 5% w/v dodeca-molybdophosphoric acid in ethanol or an aqueous potassium permanganate solutions, as appropriate, followed by heating. Enantiomeric excesses were determined by using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard Series 1050 system.

3) Melting points

Melting points were recorded on a Gallenkamp or Leica-Galen III apparatus and remain uncorrected.

4) Infrared Spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR or Perkin Elmer Spectrum RX1 FTIR spectrometer deposited as thin film on a sodium chloride plate, with absorption maxima (ν_{max}) recorded in cm^{-1}, and labelled as broad (br), strong (s), medium (m), or weak (w). Only selected absorbencies are reported.

5) NMR Spectroscopy

All ^{1}H and ^{13}C NMR spectra were recorded using Bruker 500 MHz, 400 MHz and 300 MHz spectrometers, and a Varian 300 MHz spectrometer using the solvent $SiMe_4$ as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are reported in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: ---/ ppm (multiplicity, number of protons, coupling constants *J* / Hz, and assignment). Multiplicities are recorded as a singlet (s), apparent singlet (app. s), broad singlet (br s), doublet (d), apparent doublet (app. d), triplet (t), apparent triplet (app. t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), pentet (p), or multiplet (m). DEPT135 and two-dimensional NMR spectroscopy (COSY, HMQC, HMBC) were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

6) Mass Spectra

Low resolution mass spectra were recorded on a Micromass Trio 2000 quadropole mass spectrometer (electron impact (EI), chemical ionisation (CI)) or a Micromass Platform II spectrometer (electrospray) using electrospray ionisation (ES) in the positive and negative mode. Selected mass-to-charge peaks (*m/z*) are quoted in Daltons as a percentage of the base peak. High resolution mass spectra were recorded on a Thermo Finnigan Mat 95XP mass spectrometer using electrospray ionisation (ES).

7) X-ray Crystallographic Data

X-ray crystallographic data was measured on a Bruker Smart Apex CCD diffractometer. Crystals were mounted on drop of fomblin (perfluoromethyl isopropyl ether) oil in a Hamilton Cryoloop.

8) Polarimetry

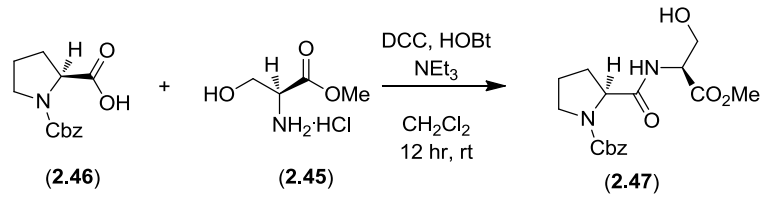
Optical rotations were recorded using an Optical Activity AA-1000 or Perkin Elmer 241 polarimeter; specific rotations ($[\alpha]_D^t$) were calculated by $100\alpha/(cl)$, in which, *c* (concentration) is quoted in g/100 mL; *l* equals to 0.5 dm or 1.0 dm; *D* refers to the D-line of sodium (589 nm); temperature (*t*) is given in degrees Celsius (ºC).

Where a compound has been synthesised more than once in different enantioselectivity, the optical rotation is quoted for the compound with the greatest enantioselectivity.

7.2 Experimental for chapter 2

7.2.1 Synthesis of α,β-unsaturated amide (**2.51**)

7.2.1.1 Synthesis and characterisation of benzyl (2*S*)-2-[(3*S*)-3-(hydroxymethyl)-4-methoxy-4-oxobutanoyl]pyrrolidine-1-carboxylate (**2.47**)[34]

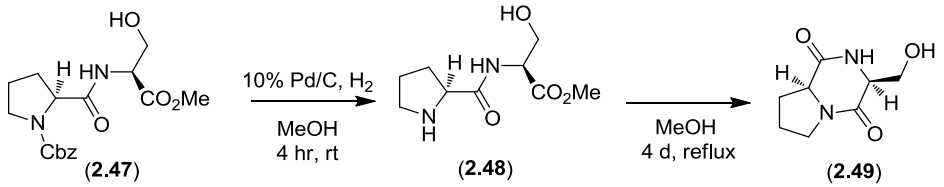


(**2.46**) (**2.45**) (**2.47**)

To a solution of L-serine methyl ester hydrochloride (2.00 g, 14 mmol) in CH_2Cl_2 (15 mL) at 0 °C under N_2 were added NEt_3 (2.2 ml, 16 mmol), Cbz-protected L-proline (3.50 g, 14 mmol) and HOBt (2.10 g, 16 mmol). The solution was stirred at 0 °C under N_2 for 15 minutes before the addition of DCC (3.20 g, 16 mmol). After stirring at room temperature for 12 hours the reaction mixture was filtered to remove the dicyclohexyl urea and the residue was washed with CH_2Cl_2 (3 x 20 mL). The solution was washed with a 10% $NaHCO_3$ solution (30 mL) and the aqueous layer then extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were washed with brine (40 mL) and a 5% HCl solution (30 mL). The acidic layer was washed with CH_2Cl_2 (5 x 20 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the crude product (5.36 g). This was purified by flash silica gel chromatography using EtOAc to give the title compound as a set of rotamers (1 : 1) as a colourless solid (3.15 g, 64%).

M.P. 98-100 °C (lit. 103-107 °C); **$[\alpha]_D^{25}$** = - 18.9 (c = 2.00 in $CHCl_3$) (lit. $[\alpha]_D^{25}$ = -29.0 (c = 2.00 in $CHCl_3$)); **^{1}H NMR: δ_H** (500 MHz, CD_3OD) 1.81-1.90 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.93-2.00 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.03-2.10 (m, 1H, $NCH_2CH_2C\underline{H}_AH_B$), 2.16-2.31 (m, 1H, $NCH_2CH_2CH_A\underline{H}_B$), 3.45-3.53 (m, 1H, $NC\underline{H}_AH_BCH_2$), 3.56-3.64 (m, 1H, $NCH_A\underline{H}_BCH_2$), 3.69 (s, 3H, $CO_2C\underline{H}_3$, rotamer at 3.72 ppm), 3.83-3.98 (m, 2H, $CHC\underline{H}_2OH$), 4.42 (dd, 1H, *J* = 8.5 Hz, *J* = 3.9 Hz, $C\underline{H}CH_2CH_2$), 4.50-4.61 (m, 1H, $NHC\underline{H}CO_2CH_3$), 5.06-5.17 (m, 2H, $CO_2C\underline{H}_2$), 7.26-7.41 (m, 5H, 5 x Ar-H); **^{13}C NMR: δ_C** (125 MHz, CD_3OD) 24.7 ($NCH_2\underline{C}H_2CH_2$, rotamer at 25.2 ppm), 31.5 ($NCH_2CH_2\underline{C}H_2$, rotamer at 32.6 ppm), 48.3 ($N\underline{C}H_2CH_2$, rotamer at 48.7 ppm), 53.1 ($CO_2\underline{C}H_3$), 56.1 ($\underline{C}HCH_2OH$, rotamer at 56.2 ppm), 61.3 ($\underline{C}HCH_2CH_2$, rotamer at 61.6 ppm), 63.0 ($\underline{C}H_2OH$), 68.3 ($CO_2\underline{C}H_2$), 128.8 (Ar$\underline{C}$-H), 129.0 (Ar$\underline{C}$-H), 129.1 (Ar$\underline{C}$-H), 129.6 (Ar$\underline{C}$-H), 129.7 (Ar$\underline{C}$-H), 138.2 (Ar$\underline{C}$-quat), 156.4 (CO, rotamer at 156.8 ppm), 172.3 (CO, rotamer at 172.8 ppm), 175.0 (CO, rotamer at 175.4 ppm).

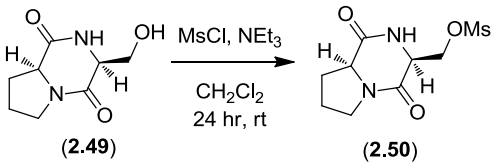
7.2.1.2 Synthesis and characterisation of (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.49**)[34]



To a flask containing Pd/C (1.18 g) under N_2 was added a solution of protected dipeptide (**2.47**) (11.8 g, 0.034 mol) in MeOH (500 mL) under N_2. The system was flushed with H_2 and stirred overnight at room temperature under an atmosphere of H_2. The reaction mixture was filtered through a Celite® pad and washed with MeOH (3 x 100 mL) before reduction of the solvent *in vacuo* to approximately 500 ml. The solution was heated to reflux for 4 days before evaporating the solvent *in vacuo* to afford the crude product. The crude was triturated with CH_2Cl_2 (100 mL) to afford the product (3.67 g, 59%) as a colourless solid.

M.P. 128-131 °C (lit. 134-136 °C); $\mathbf{[\alpha]_D^{25}}$ = -65.1 (c = 2.17 in DMSO) (lit. $[\alpha]_D^{25}$ = -114.8 (c = 2.00 in DMSO); **^{1}H NMR: δ_H** (500 MHz, D_6-DMSO) 1.76-1.89 (m, 3H, $NCH_2C\underline{H}_2CH_2$, $NCH_2CH_2C\underline{H}_AH_B$), 2.09-2.17 (m, 1H, $NCH_2CH_2CH_A\underline{H}_B$), 3.40-3.47 (m, 2H, $NC\underline{H}_2CH_2$), 3.66-3.75 (m, 2H, $C\underline{H}_2OH$), 4.03 (t, 1H, *J* = 3.6 Hz, $C\underline{H}CH_2OH$), 4.14 (app. t, 1H, *J* = 7.5 Hz, $NC\underline{H}CH_2$), 4.72 (t, 1H, *J* = 5.8 Hz, $CH_2O\underline{H}$), 7.82 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, D_6-DMSO) 22.3 ($NCH_2\underline{C}H_2CH_2$), 29.5 ($NCH_2CH_2\underline{C}H_2$), 45.6 ($N\underline{C}H_2CH_2$), 59.0 ($\underline{C}HCH_2OH$), 60.4 ($N\underline{C}HCH_2$), 64.3 ($\underline{C}H_2OH$), 165.4 (CO), 169.9 (CO).

7.2.1.3 Synthesis and characterisation of [(3*S*,8a*S*)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]methyl methanesulfonate **(2.50)**

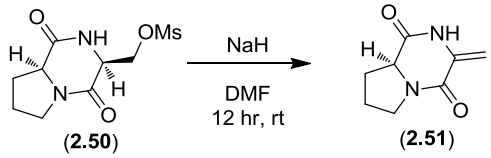


To a solution of primary alcohol (**2.49**) (100 mg, 0.54 mmol) in dry CH_2Cl_2 (3 mL) under N_2 was added anhydrous NEt_3 (90 µl, 0.65 mmol). The solution was cooled to 0 °C and a solution of MsCl (42 µL, 0.55 mmol) in dry CH_2Cl_2 (2 ml) under N_2 was added. The solution was warmed to room temperature and stirred for 24 hours before evaporation of the solvent *in vacuo* to obtain the crude product. Flash silica gel chromatography with increasing polarity from dichloromethane to dichloromethane : methanol, 9 : 1 afforded the product (116 mg, 82%) as a colourless solid.

M.P. 122-124°C; $\mathbf{[\alpha]_D^{26}}$ = - 88.0 (c = 0.55 in MeOH); **ν_{max}(film)/cm^{-1}** 3235 (br w, N-H), 1685 (s, C=O), 1646 (s, C=O), 1350 (s, S=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.82-1.91 (m, 1H, $NCH_2CH_2C\underline{H}_AH_B$), 1.96-2.08 (m, 2H, $NCH_2CH_2CH_A\underline{H}_B$, $NCH_2C\underline{H}_AH_B$), 2.28-2.35 (m, 1H, $NCH_2CH_A\underline{H}_B$), 3.05 (s, 3H, $SO_2C\underline{H}_3$), 3.47-3.60 (m, 2H, $NC\underline{H}_2CH_2$), 4.07-4.11 (m, 1H,

NC<u>H</u>CH$_2$CH$_2$), 4.33-4.36 (m, 1H, C<u>H</u>CH$_2$OH), 4.49 (dd, 1H, *J* = 10.9 Hz, *J* = 3.2 Hz, CHC<u>H$_A$H$_B$</u>OH), 4.64 (dd, 1H, *J* = 10.9 Hz, *J* = 3.2 Hz, CHCH$_A$<u>H$_B$</u>OH), 7.14 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, $CDCl_3$) 22.1 (NCH$_2$<u>C</u>H$_2$CH$_2$), 29.4 (NCH$_2$CH$_2$<u>C</u>H$_2$), 38.0 (SO$_2$<u>C</u>H$_3$), 46.0 (N<u>C</u>H$_2$CH$_2$), 57.6 (<u>C</u>HCH$_2$OH), 58.7 (N<u>C</u>HCH$_2$CH$_2$), 70.7 (CH<u>C</u>H$_2$OH), 162.1 (CO), 169.4 (CO); ***m/z* (ES$^+$)** 285 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 285.0522 for $C_9H_{14}N_2O_5SNa^+$ [M+Na]$^+$, requires 285.0516.

7.2.1.4 Synthesis and characterisation of (8a*S*)-3-methylenehexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **(2.51)**



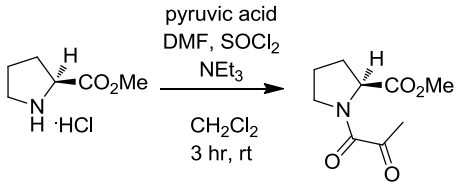
(**2.50**) (**2.51**)

To a flask containing sodium hydride (8.4 mg, 0.35 mmol) at 0 °C under N_2 was added a solution of mesylated primary alcohol (**2.50**) (84 mg, 0.32 mmol) in DMF (4 mL) at 0 °C under N_2. The solution was stirred at 0 °C for 30 minutes before being warmed to room temperature and stirring for 12 hours. The solution was quenched with 5% aqueous HCl until neutral and the solvent evaporated *in vacuo*. MeOH (5 mL) was added to the solid which was subsequently filtered before evaporating the solvent *in vacuo* to form the crude. Flash silica gel chromatography using dichloromethane : methanol, 9.5 : 0.5 afforded the product (38 mg, 71%) as a colourless solid.

M.P. 244-246 °C (dec.); **$[\alpha]_D^{32}$** = - 10.0 (c = 0.64 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3195 (br w, N-H), 1671 (s, C=O), 1630 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.82-1.97 (m, 2H, NCHC<u>H$_2$</u>), 1.99-2.05 (m, 1H, NCH$_2$C<u>H$_A$H$_B$</u>), 2.35-2.41 (m, 1H, NCH$_2$CH$_A$<u>H$_B$</u>), 3.49-3.55 (m, 1H, N<u>C</u>H$_A$H$_B$), 3.69-3.76 (m, 1H, NCH$_A$<u>H$_B$</u>), 4.16 (dd, 1H, *J* = 10.4 Hz, *J* = 6.3 Hz, NC<u>H</u>CH$_2$), 4.82 (app. s, 1H, C<u>H$_A$H$_B$</u>CC(O)), 5.53 (app. s, 1H, CH$_A$<u>H$_B$</u>CC(O)), 8.35 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, D_6-DMSO) 22.0 (CH<u>C</u>H$_2$), 29.3 (NCH$_2$<u>C</u>H$_2$), 45.7 (N<u>C</u>H$_2$CH$_2$), 59.6 (<u>C</u>HCH$_2$), 99.9 (<u>C</u>H$_2$CC(O)), 137.1 (CH$_2$<u>C</u>C(O)), 157.4 (CO), 166.8 (CO); ***m/z* (ES$^-$)** 165 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 189.0634 for $C_8H_{10}N_2O_2Na^+$ [M+Na]$^+$, requires 189.0634.

7.2.2 Synthesis of α,β-unsaturated amide (**2.51**) via tertiary alcohol (**2.53**)

7.2.2.1 Synthesis and characterisation of methyl 1-acetoacetyl-L-prolinate (**2.52**)



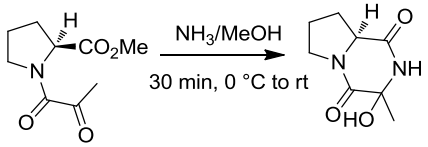
(**2.52**)

A solution of pyruvic acid (0.57 mL, 8.2 mmol), anhydrous DMF (0.51 mL, 6.6 mmol) and $SOCl_2$ (0.70 mL, 9.0 mmol) was stirred at room temperature for 2 hours under N_2. A solution of L-proline

methyl ester hydrochloride (680 mg, 4.1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise, followed by NEt_3 (1.9 mL, 14 mmol) in dry CH_2Cl_2 (5 mL). The solution was stirred for 1 hour at room temperature before being poured into a separating funnel containing distilled water (20 mL) and extracting with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the product as a yellow oil existing as two rotamers (1 : 1.6) (802 mg, 98%) which did not require further purification.

$[\alpha]_D^{25}$ = - 69.3 (c = 3.49 in MeOH); **ν_{max}(film)/cm^{-1}** 1745 (s, C=O), 1716 (s, C=O), 1638 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.78-1.86 (m, 1H, $NCH_2CH_AH_B$, rotamer at 2.01 ppm), 1.87-1.94 (m, 1H, $NCH_2CH_AH_B$, rotamer at 2.01 ppm), 2.14-2.23 (m, 1H, $NCHCH_AH_B$, rotamer at 2.01 ppm) 2.27-2.36 (m, 1H, $NCHCH_AH_B$, rotamer at 2.18 ppm), 2.45 (s, 3H, $C(O)CH_3$, rotamer at 2.43 ppm), 3.54-3.61 (m, 1H, $NCH_AH_BCH_2$, rotamer at 3.72 ppm), 3.68-3.76 (m, 3H, CO_2CH_3, rotamer at 3.75 ppm), 3.77-3.87 (m, 1H, $NCH_AH_BCH_2$, rotamer underneath), 4.85-4.89 (m, 1H, $NCHCH_2$, rotamer at 4.50 ppm); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.1 (NCH_2CH_2, rotamer at 25.3 ppm), 26.6 ($C(O)CH_3$, rotamer at 27.1 ppm), 31.4 ($NCHCH_2$, rotamer at 28.6 ppm), 47.5 (NCH_2CH_2, rotamer at 48.2 ppm), 52.6 (CO_2CH_3, rotamer at 52.4 ppm), 59.6 ($NCHCH_2$), 162.7 (CO, rotamer at 162.0 ppm), 172.7 (CO, rotamer at 171.9 ppm), 198.3 (CO, rotamer at 197.6 ppm); ***m/z* (ES$^+$)** 222 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 222.0741 for $C_9H_{13}NO_4Na^+$ [M+Na]$^+$, requires 222.0737.

7.2.2.2 Synthesis and characterisation of (8a*S*)-3-hydroxy-3methylhexahydropyrrolo[1,2*a*]pyrazine-1,4-dione (**2.52**)



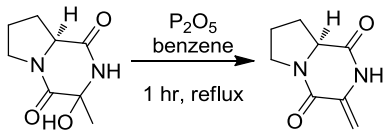
(**2.52**) (**2.53**)

Anhydrous NH_3 was bubbled through a solution of proline methyl ester derivative (**2.52**) (403 mg, 2.0 mmol) in distilled MeOH (7 mL) at 0 °C for 30 minutes before warming the solution to room temperature and stirring under a NH_3 atmosphere for 1 hour. The reaction was monitored by TLC analysis and on completion the solvent was evaporated *in vacuo* to afford the crude product as a yellow solid. Purification by flash silica gel chromatography with increasing polarity from dichloromethane to dichloromethane : methanol, 9.5 : 0.5 afforded the product (350 mg, 84%) as a colourless solid and as a mixture of diastereomers (8:1).

M.P. 156-158 °C; **$[\alpha]_D^{26}$** = - 39.0 (c = 1.11 in MeOH); **ν_{max}(film)/cm^{-1}** 3319 (br w, N-H, O-H), 1684 (m, C=O), 1646 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, CD_3OD) 1.47 (s, 3H, CCH_3), 1.78-1.89 (m, 2H, $NCHCH_2$), 1.90-1.98 (m, 1H, $NCH_2CH_AH_B$), 2.20-2.29 (m, 1H, $NCH_2CH_AH_B$), 3.38-3.48 (m, 2H, NCH_2), 4.27 (dd, 1H, *J* = 9.9 Hz, *J* = 6.6 Hz, $CHCH_2$, minor diastereomer at 4.19 ppm); **^{13}C NMR: δ_C** (75 MHz, D_6-DMSO) 22.8 ($NCHCH_2$, minor diastereomer at 22.7 ppm), 24.6 (CCH_3, minor diastereomer), 29.0 (NCH_2CH_2, minor diastereomer at 29.4 ppm), 45.7 (NCH_2CH_2), 59.5 ($NCHCH_2$), 80.7 (CCH_3, minor diastereomer at 81.5 ppm), 166.1 (CO, minor diastereomer at 167.6

ppm), 171.7 (CO, minor diastereomer at 171.6 ppm); ***m/z* (ES$^+$)** 207 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 207.0733 for $C_8H_{12}N_2O_3Na^+$ [M+Na]$^+$, requires 207.0740.

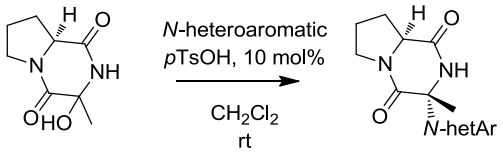
7.2.2.3 Synthesis of (8a*S*)-3-methylenehexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.51**)



(**2.53**) (**2.51**)

To a solution of tertiary alcohol (**2.53**) (92 mg, 0.5 mmol) in dry toluene (10 mL) under N_2 was added P_2O_5 (142 mg, 1.0 mmol) and the solution was refluxed for 1 hour. While still hot the solution was filtered though a cotton wool plug and the solvent evaporated *in vacuo* to afford the product (80 mg, 96%) as a colourless solid which did not require further purification. The spectroscopic data of the titled product was identical to that previously described (**7.2.1.4**).

7.2.3 Diastereoselective addition reactions of *N*-heteroaromatics to DKP (**2.53**)

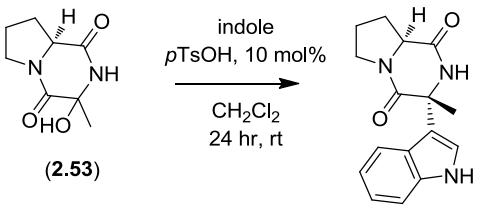


(**2.53**)

General procedure for the addition of *N*-heteroaromatics to DKP (2.53)

To a solution of DKP (**2.53**) (1 equivalent) in anhydrous CH_2Cl_2 (8 mL/mmol) under N_2, was added the *N*-heteroatomatic compound (1.2 equivalents) and *p*-TsOH (10 mol%) and the solution was stirred at room temperature until completion of the reaction. NEt_3 (50 mol%) was added to the reaction and the solvent evaporated *in vacuo* to afford the crude reaction mixture which was purified by flash silica gel chromatography.

7.2.3.1 Synthesis and characterisation of 3-(1*H*-indol-3-yl)-3-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.54**)



(**2.53**) (**2.54**)

Following the general procedure (0.3 mmol scale) the titled compound (as separable mixtures of diastereomers (4.5 : 1) was obtained after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (ethyl acetate) (major: 67 mg, minor: 14 mg, 95%). The dr was determined by analysis of the crude ^{1}H NMR. The major diastereomer was recrystalised (EtOAc/petroleum ether) and the relative configuration was proved by X-ray analysis.

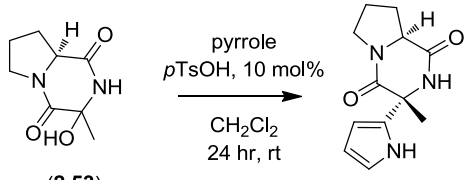
MAJOR

M.P. 198-200 °C (dec.); **$[\alpha]_D^{29}$** = - 20.6 (c = 0.62 in MeOH); **ν_{max}(film)/cm^{-1}** 3256 (br m, N-H), 1642 (br s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.56-1.65 (m, 1H, NCHC$\underline{H}_A\underline{H}_B$), 1.81-1.90 (m, 4H, C$\underline{H}_3$, NCHC$H_A\underline{H}_B$), 1.97-2.06 (m, 1H, NC$H_2C\underline{H}_A\underline{H}_B$), 2.14-2.20 (m, 1H, NC$H_2CH_A\underline{H}_B$), 3.30-3.39 (m, 1H, NC$\underline{H}_A\underline{H}_BCH_2$), 3.51-3.58 (m, 1H, NC$H_A\underline{H}_BCH_2$), 3.86 (dd, 1H, *J* = 9.6 Hz, *J* = 7.3 Hz, NC$\underline{H}$CH_2), 6.99 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.01-7.06 (m, 1H, Ar-H), 7.13 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.28 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.49 (br s, 1H, N-H), 7.91 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.75 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.6 (NCH$\underline{C}H_2$), 25.6 (C$\underline{C}H_3$), 28.5 (NC$H_2\underline{C}H_2$), 45.9 (N$\underline{C}H_2$CH_2), 58.9 (N$\underline{C}$HCH_2), 60.5 (C$H_3\underline{C}$), 111.5 (Ar$\underline{C}$-H), 116.8 (Ar$\underline{C}$-quat), 120.2 (Ar$\underline{C}$-quat), 120.6 (Ar$\underline{C}$-H), 121.0 (Ar$\underline{C}$-H), 122.7 (Ar$\underline{C}$-H), 124.4 (Ar$\underline{C}$-quat), 137.3 (Ar$\underline{C}$-quat), 167.1 (CO), 171.8 (CO); ***m/z* (ES$^+$)** 306 ([M+Na]$^+$, 100%); **HRMS EI (+)** Found 306.1210 for $C_{16}H_{17}N_3O_2Na^+$ [M+Na]$^+$, requires 306.1213.

MINOR

M.P. 130-134°C; **$[\alpha]_D^{25}$** = - 20.7 (c = 0.60 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3253 (br m, N-H), 1652 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.53-1.74 (m, 1H, NCHC$\underline{H}_A\underline{H}_B$), 1.82-1.95 (m, 4H, C$\underline{H}_3C, NCH_2C\underline{H}_A\underline{H}_B$), 1.99-2.08 (m, 1H, NC$H_2CH_A\underline{H}_B$), 2.23-2.30 (m, 1H, NCHC$H_A\underline{H}_B$), 3.54-3.61 (m, 1H, NC$\underline{H}_A\underline{H}_BCH_2$), 3.65-3.73 (m, 1H, NC$H_A\underline{H}_BCH_2$), 4.18 (dd, 1H, *J* = 10.6 Hz, *J* = 6.5 Hz, NC$\underline{H}$CH_2), 6.64 (d, 1H, *J* = 2.6 Hz, NHC$\underline{H}$), 7.06-7.16 (m, 4H, 3 x Ar-H, N-H), 7.33-7.37 (m, 1H, Ar-H), 9.19 (br d, 1H, *J* = 1.8 Hz, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 22.2 (NC$H_2\underline{C}H_2$), 24.9 ($\underline{C}H_3$C), 28.8 (NCH$\underline{C}H_2$), 45.9 (N$\underline{C}H_2$CH_2), 58.8 (N$\underline{C}$HCH_2), 59.7 (C$H_3\underline{C}$), 111.8 (Ar$\underline{C}$-H), 114.7 (Ar$\underline{C}$-quat), 119.3 (Ar$\underline{C}$-H), 119.4 (Ar$\underline{C}$-H), 121.9 (Ar$\underline{C}$-H), 124.0 (NH$\underline{C}$H), 124.8 (Ar$\underline{C}$-quat), 137.1 (Ar$\underline{C}$-quat), 168.3 (CO), 169.0 (CO); ***m/z* (ES$^+$)** 306 ([M+Na]$^+$, 35%), 589 ([M+Na]$^+$, 70%); **HRMS EI (+)** Found 306.1213 for $C_{16}H_{17}N_3O_2Na^+$ [M+Na]$^+$, requires 306.1213.

7.2.3.2 Synthesis and characterisation of 3-methyl-3-(1*H*-pyrrol-2-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.55**)



(**2.53**) (**2.55**)

Following the general procedure (0.61 mmol scale) the titled compound (as separable mixtures of diastereomers (3.2 : 1) was obtained after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1

: 1 to ethyl acetate) (major: 117 mg, minor: 23 mg, 98%). The dr was determined by analysis of the crude ^{1}H NMR. The major diastereomer was recrystalised (EtOAc) and the relative configuration was proved by X-ray analysis.

MAJOR

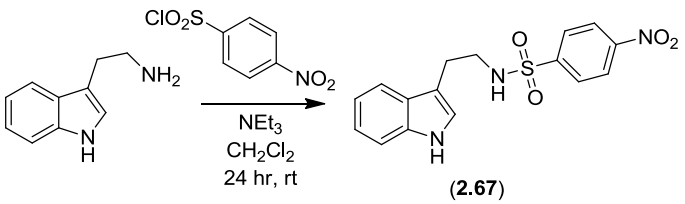
M.P. 220-224 ºC; **$[\alpha]_D^{25}$** = - 44.0 (c = 1.38 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3253 (br w, N-H), 1654 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.70 (s, 3H, CH_3C), 1.71-1.83 (m, 1H, $NCH_2CH_AH_B$), 1.91-2.06 (m, 2H, $NCH_2CH_AH_B$, $NCHCH_AH_B$), 2.23-2.32 (m, 1H, $NCHCH_AH_B$), 3.42 (ddd, 1H, *J* = 11.6 Hz, *J* = 9.1 Hz, *J* = 2.7 Hz, $NCH_AH_BCH_2$), 3.50-3.57 (m, 1H, $NCH_AH_BCH_2$), 3.95 (dd, 1H, *J* = 10.0 Hz, *J* = 6.7 Hz, $NCHCH_2$), 6.05 (app. t, 2H, *J* = 2.4 Hz, NHCHCHCH, NHCHCHCH), 6.19 (br s, 1H, N-H), 6.71 (dd, 1H, *J* = 4.6 Hz, *J* = 2.4 Hz, NHCH), 8.51 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 22.4 (NCH_2CH_2), 26.5 (CH_3C), 28.5 ($NCHCH_2$), 45.7 (NCH_2CH_2), 58.7 ($NCHCH_2$), 59.8 (CH_3C), 105.0 & 108.1 (NHCHCHCH, NHCHCHCH), 119.4 (NHCH), 130.7 (ArC-quat), 166.4 (CO), 170.3 (CO); ***m/z* (ES$^+$)** 256 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 256.1049 for $C_{12}H_{15}N_3O_2Na^+$ [M+Na]$^+$, requires 256.1056.

MINOR

M.P. 48-53 ºC; **$[\alpha]_D^{25}$** = - 33.3 (c = 0.81 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3267 (br w, N-H), 1655 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.76 (s, 3H, CH_3C), 1.81-2.04 (m, 3H, $NCH_2CH_2CH_2$, $NCHCH_AH_B$), 2.36-2.41 (m, 1H, $NCHCH_AH_B$), 3.48 (ddd, 1H, *J* = 12.1 Hz, *J* = 9.2 Hz, *J* = 2.7 Hz, $NCH_AH_BCH_2CH_2$), 3.56-3.62 (m, 1H, $NCH_AH_BCH_2CH_2$), 4.13 (dd, 1H, *J* = 10.1 Hz, *J* = 6.5 Hz, $NCHCH_2$), 6.07-6.10 (m, 2H, NHCCHCH, NHCCHCH), 6.49 (br s, 1H, N-H), 6.70-6.72 (m, 1H, NHCHCH), 9.31 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 22.0 (NCH_2CH_2), 27.2 (CH_3C), 29.2 ($NCHCH_2$), 45.8 (NCH_2CH_2), 58.8 ($NCHCH_2$), 59.7 (CH_3C), 105.6 & 107.9 (NHCHCHCH, NHCHCHCH), 118.9 (NHCH), 131.0 (ArC-quat), 167.1 (CO), 168.1 (CO); ***m/z* (ES$^+$)** 256 ([M+Na]$^+$, 40%); **HRMS ES (+)** Found 256.1063 for $C_{12}H_{15}N_3O_2Na^+$ [M+Na]$^+$, requires 256.1056.

7.2.4 Synthesis of tryptamine and diketopiperazine starting materials

7.2.4.1 Synthesis and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-4-nitrobenzenesulfonamide (**2.67**)

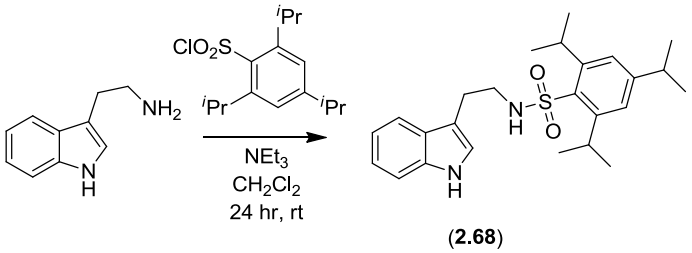


(**2.67**)

To a solution of tryptamine (900 mg, 5.6 mmol) in CH_2Cl_2 (10 mL) at room temperature, was added 4-nitrobenzenesulfonyl chloride (1.24 g, 5.6 mmol) and NEt_3 (0.78 mL, 5.6 mmol) and the solution was stirred at room temperature for 24 hours before being quenched with 1 M aqueous HCl (10 mL). The biphasic solution was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, before evaporating the solvent *in vacuo* to afford the product (1.60 g, 83%) as a brown solid which did not require further purification.

M.P. 128-132 ºC; **ν_{max}(film)/cm^{-1}** 3411 (br w, N-H), 1528 (s, N-O), 1349 (s, N-O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 2.80 (t, 2H, *J* = 7.2 Hz $NCH_2C\underline{H}_2$), 3.09-3.16 (m, 2H, $NC\underline{H}_2CH_2$), 6.92 (t, 1H, *J* = 7.4 Hz, Ar-H indole), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.09 (d, 1H, *J* = 1.4 Hz, NHC<u>H</u>), 7.25 (d, 1H, *J* = 8.0 Hz, Ar-H indole), 7.36 (d, 1H, *J* = 7.8 Hz, Ar-H indole), 7.91 (d, 2H, *J* = 8.7 Hz, 2 x Ar-H), 8.12 (t, 1H, *J* = 5.5 Hz, $N\underline{H}CH_2$), 8.26 (d, 2H, *J* = 8.7 Hz, 2 x Ar-H), 10.79 (br s, 1H, N-H indole); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 26.2 ($NCH_2\underline{C}H_2$), 44.2 ($N\underline{C}H_2CH_2$), 111.5 (Ar<u>C</u>-quat), 112.2 (Ar<u>C</u>-H indole), 118.8 (Ar<u>C</u>-H indole), 119.1 (Ar<u>C</u>-H indole), 121.7 (Ar<u>C</u>-H indole), 124.0 (Ar<u>C</u>-H indole), 125.1 (2 x Ar<u>C</u>-H), 127.7 (Ar<u>C</u>-quat), 128.6 (2 x Ar<u>C</u>-H), 137.0 (Ar<u>C</u>-quat), 147.0 (Ar<u>C</u>-quat), 150.0 (Ar<u>C</u>-quat); ***m/z* (ES$^+$)** 368 ([M+Na]$^+$, 52%), 492 (100%); **HRMS ES (+)** Found 368.0677 for $C_{16}H_{15}N_3O_4SNa^+$ [M+Na]$^+$, requires 368.0675.

7.2.4.2 Synthesis and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-2,4,6-triisopropylbenzenesulfonamide (**2.68**)

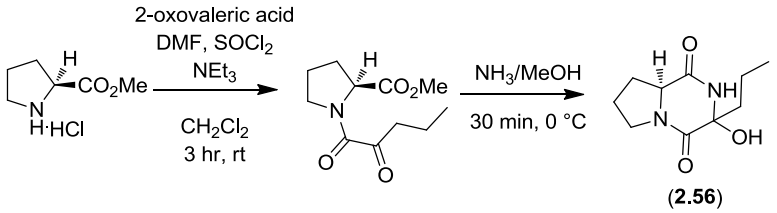


(**2.68**)

To a solution of tryptamine (373 mg, 2.32 mmol) in CH_2Cl_2 (10 mL) at room temperature, was added 2,4,6-triisopropylbenzenesulfonyl chloride (703 mg, 2.32 mmol) and triethylamine (0.32 mL, 2.32 mmol) and the solution was stirred at room temperature for 24 hours before being quenched with 1 M aqueous HCl (10 mL). The biphasic solution was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, before evaporating the solvent *in vacuo* to afford the product (925 mg, 93%) as a brown solid which did not require further purification.

M.P. 126-130 ºC; **ν_{max}(film)/cm^{-1}** 3387 (br w, N-H), 1317 (br m, S=O), 1150 (br s, S-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.19 (d, 12H, *J* = 6.7 Hz, 4 x $C\underline{H}_3CH$), 1.26 (d, 6H, *J* = 6.8 Hz, 2 x $C\underline{H}_3CH$), 2.86-2.93 (m, 1H, $(CH_3)_2C\underline{H}$), 3.02 (t, 2H, *J* = 6.6 Hz, $NHCH_2C\underline{H}_2$), 3.29 (t, 2H, *J* = 6.6 Hz, $NHC\underline{H}_2CH_2$), 4.07-4.15 (m, 2H, 2 x $(CH_3)_2C\underline{H}$), 4.41 (br s, 1H, N-H), 7.03 (s, 1H, NHC<u>H</u>C), 7.08 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.14 (s, 2H, 2 x C<u>H</u>CCH), 7.19 (t, 1H, *J* = 7.6 Hz, Ar-H indole), 7.37 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.49 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 8.13 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 23.6 (2 x $(CH_3)_2\underline{C}H$), 24.7 (2 x $(\underline{C}H_3)_2CH$), 25.6 ($NCH_2\underline{C}H_2$), 29.6 ($(\underline{C}H_3)_2CH$), 34.1 ($(CH_3)_2\underline{C}H$), 42.9 ($N\underline{C}H_2CH_2$), 111.3 & 111.8 (Ar<u>C</u>-quat, Ar<u>C</u>-H), 118.5 (Ar<u>C</u>-H), 119.6 (Ar<u>C</u>-H), 122.3 (Ar<u>C</u>-H), 122.5 (Ar<u>C</u>-H), 123.7 (2 x Ar<u>C</u>-H), 127.0 (Ar<u>C</u>-quat), 132.1 (Ar<u>C</u>-quat), 136.4 (Ar<u>C</u>-quat), 150.3 (2 x Ar<u>C</u>-quat), 152.6 (Ar<u>C</u>-quat); ***m/z* (ES$^-$)** 425 ([M-H]$^-$, 60%), 709 (100%); **HRMS ES (+)** Found 449.2229 for $C_{25}H_{34}N_2O_2SNa^+$ [M+Na]$^+$, requires 449.2233.

7.2.4.2 Synthesis and characterisation of (8a*S*)-3-hydroxy-3-propylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.56**)

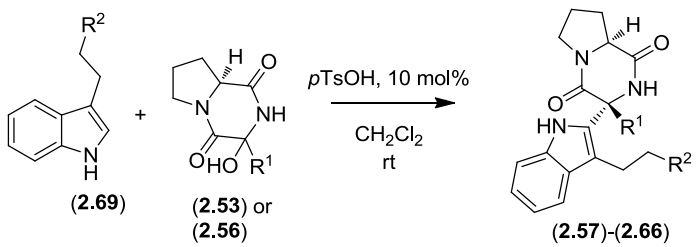


A solution of 2-oxovaleric acid (1.5 mL, 14.3 mmol), anhydrous DMF (0.88 mL, 11.5 mmol) and $SOCl_2$ (1.15 mL, 15.8 mmol) was stirred at room temperature for 2 hours under N_2. A solution of L-proline methyl ester hydrochloride (1.18 g, 7.2 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise, followed by NEt_3 (3.30 mL, 25.6 mmol) in dry CH_2Cl_2 (15 mL). The solution was stirred for 1 hour at room temperature before being poured into a separating funnel containing distilled water (30 mL) and extracting with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the crude (2.34 g) which was used in the following step without purification.

The crude was dissolved in freshly distilled MeOH (7 mL) and cooled to 0 °C where anhydrous NH_3 was bubbled through the solution for 30 minutes before warming the solution to room temperature and stirring under a NH_3 atmosphere for 1 hour. The reaction was monitored by TLC analysis and on completion the solvent was evaporated *in vacuo* to afford the crude. Trituration with ethyl acetate afforded the product as a single diastereomer (745 mg, 49% yield over 2 steps) as a colourless solid.

M.P. 172-174 ºC; **$[\alpha]_D^{25}$** = - 9.6 (c = 1.06 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3281 (br w, N-H, O-H), 1672 (s, C=O), 1653 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 0.82 (t, 3H, *J* = 7.3 Hz, C$\underline{H}_3$CH$_2$), 1.11-1.28 (m, 2H, C$\underline{H}_2$CH$_3$), 1.54-1.63 (m, 1H, C$\underline{H}_A$H$_B$CH$_2$CH$_3$), 1.69-1.93 (m, 4H, CH$_A\underline{H}_B$CH$_2$CH$_3$, NCHC$\underline{H}_A$H$_B$, NCH$_2$C$\underline{H}_2$), 2.14-2.20 (m, 1H, NCHCH$_A\underline{H}_B$), 3.30-3.45 (m, 2H, NC$\underline{H}_2$CH$_2$), 4.19 (dd, 1H, *J* = 9.7 Hz, *J* = 6.8 Hz, NC$\underline{H}$CH$_2$), 6.38 (br s, 1H, O-H), 8.70 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 14.9 (C$\underline{H}_3$), 17.9 (C$\underline{H}_2$), 22.6 (C$\underline{H}_2$), 29.3 (C$\underline{H}_2$), 31.6 (C$\underline{H}_2$), 45.6 (C$\underline{H}_2$), 59.2 (N$\underline{C}$HCH$_2$), 83.3 (C(O)$\underline{C}$NH), 165.4 (CO), 171.6 (CO); ***m/z* (ES$^+$)** 235 ([M+Na]$^+$, 45%), 447 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 235.1052 for $C_{10}H_{16}N_2O_3Na^+$ [M+Na]$^+$, requires 235.1053.

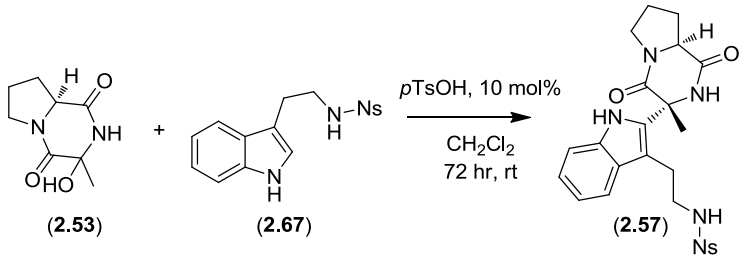
7.2.5 The addition of 3-substituted indoles to L-proline derived DKPs



General procedure for the addition of 3-substituted indoles to DKP (2.53) or (2.56)

To a solution of DKP (**2.53**) or (**2.56**) (1 equivalent) in anhydrous CH_2Cl_2 (8 mL/mmol) under N_2, was added the 3-substituted indole compound (1.2 equivalents) and *p*-TsOH (10 mol%) and the solution was stirred at room temperature until completion of the reaction. NEt_3 (50 mol%) was added to the reaction and the solvent evaporated *in vacuo* to afford the crude reaction mixture which was purified by flash silica gel chromatography.

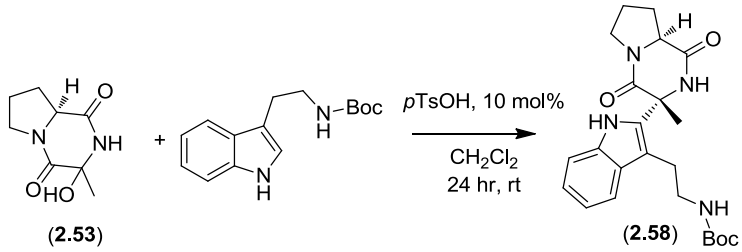
7.2.5.1 Synthesis and characterisation of *N*-(2-{2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)-4-nitrobenzenesulfonamide (**2.57**)



Following the general procedure (0.54 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 27) was obtained after 72 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (260 mg, 94%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 130-135 ºC; **$[\alpha]_D^{25}$** = - 41.1 (c = 1.09 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3273 (br w, N-H), 1675 (s, C=O), 1608 (s, C=O) 1582 (s, N=O), 1349 (s, N-O), 1309 (br s, S=O), 1161 (s, S-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.72-1.83 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.86 (s, 3H, $C\underline{H}_3C$), 1.99-2.04 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.06-2.14 (m, 1H, $NCHC\underline{H}_AH_B$), 2.29-2.32 (m, 1H, $NCHCH_A\underline{H}_B$), 2.92 (dt, 1H, *J* = 14.7 Hz, *J* = 5.6 Hz, $NCH_2C\underline{H}_AH_BC$), 3.13 (dt, 1H, *J* = 14.7 Hz, *J* = 10.1 Hz, $NCH_2CH_A\underline{H}_BC$), 3.23 (dd, 2H, *J* = 10.1 Hz, *J* = 5.6 Hz, $NC\underline{H}_2CH_2C$), 3.52 (ddd, 1H, *J* = 11.9 Hz, *J* = 8.9 Hz, *J* = 2.7 Hz, $NC\underline{H}_AH_BCH_2CH_2$), 3.57-3.64 (m, 1H, $NCH_A\underline{H}_BCH_2CH_2$), 3.91 (dd, 1H, *J* = 9.8 Hz, *J* = 7.1 Hz, $NC\underline{H}CH_2$), 5.92 (br s, 1H, $N\underline{H}SO_2$), 6.98 (t, 1H, *J* = 7.4 Hz, Ar-H indole), 7.07 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.13 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.24 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 7.61 (d, 2H, *J* = 8.6 Hz, 2 x Ar-H), 7.92 (d, 2H, *J* = 8.6 Hz, 2 x Ar-H), 8.05 (br s, 1H, N-H), 8.84 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 22.9 ($\underline{C}H_2$), 24.1 ($NCH_2\underline{C}H_2C$), 27.0 ($\underline{C}H_3C$), 28.5 ($\underline{C}H_2$), 43.5 ($N\underline{C}H_2CH_2C$), 46.6 ($N\underline{C}H_2CH_2CH_2$), 59.2 ($NH\underline{C}HCH_2$), 61.0 ($CH_3\underline{C}$), 108.5 (Ar$\underline{C}$-quat), 111.7 (Ar$\underline{C}$-H indole), 118.6 (Ar$\underline{C}$-H indole), 120.3 (Ar$\underline{C}$-H indole), 123.3 (Ar$\underline{C}$-H indole), 123.9 (2 x Ar$\underline{C}$-H), 127.9 (2 x Ar$\underline{C}$-H), 128.2 (Ar$\underline{C}$-quat), 132.4 (Ar$\underline{C}$-quat), 135.6 (Ar$\underline{C}$-quat), 145.5 (Ar$\underline{C}$-quat), 149.6 (Ar$\underline{C}$-quat), 167.1 (CO), 172.0 (CO); ***m/z* (ES$^-$)** 510 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 534.1442 for $C_{24}H_{25}N_5O_6SNa^+$ $[M+Na]^+$, requires 534.1429.

7.2.5.2 Synthesis and characterisation of *tert*-butyl (2-{2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)carbamate (**2.58**)

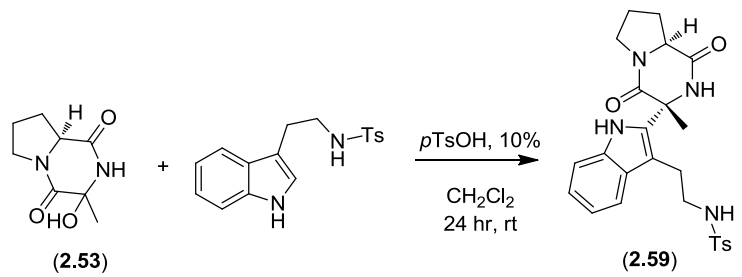


(**2.53**) (**2.58**)

Following the general procedure (0.77 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 18) was obtained after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) as a mixture of rotamers (1 : 4.6) (253 mg, 77%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 130-135 ºC; **$[\alpha]_D^{24}$** = - 18.2 (c = 0.99 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3316 (br w, N-H), 1682 (br s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.36 (br s, 9H, C(C$\underline{H}_3$)$_3$), 1.68-1.78 (m, 1H, NCHCH$_2$C$\underline{H}_A\underline{H}_B$), 1.85 (s, 3H, C$\underline{H}_3$C), 1.89-1.96 (m, 1H, NCHCH$_2$CH$_A\underline{H}_B$), 2.01-2.11 (m, 1H, NCHC$\underline{H}_A\underline{H}_B$), 2.17-2.24 (m, 1H, NCHCH$_A\underline{H}_B$), 2.91-3.05 (m, 2H, NCH$_2$C$\underline{H}_2$C), 3.18-3.25 (m, 2H, NC$\underline{H}_2$CH$_2$C), 3.45-3.50 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$CH$_2$), 3.55-3.61 (m, 1H, NCH$_A\underline{H}_B$CH$_2$CH$_2$), 3.81-3.86 (m, 1H, NC$\underline{H}$CH$_2$), 4.97 (br s, 1H, N$\underline{H}$CH$_2$CH$_2$C, rotamer at 5.64 ppm), 7.03 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.10 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.25 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.17 (br s, 1H, N-H, rotamer at 8.24 ppm), 9.03 (br s, 1H, N-H, rotamer at 8.97 ppm); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.7 (NCH$_2\underline{C}$H$_2$CH$_2$), 24.9 (NCH$_2\underline{C}$H$_2$C), 26.5 ($\underline{C}$H$_3$C), 28.1 (NCH$\underline{C}$H$_2$), 28.5 (C($\underline{C}$H$_3$)$_3$), 42.0 (N$\underline{C}$H$_2$CH$_2$C), 46.0 (N$\underline{C}$H$_2$CH$_2$CH$_2$), 58.8 (N$\underline{C}$HCH$_2$), 60.4 (C-quat, rotamer at 60.8), 79.6 (C-quat), 109.8 (Ar$\underline{C}$-quat), 111.1 (Ar$\underline{C}$-H), 118.6 (Ar$\underline{C}$-H), 119.7 (Ar$\underline{C}$-H), 122.7 (Ar$\underline{C}$-H), 128.8 (Ar$\underline{C}$-quat), 132.1 (Ar$\underline{C}$-quat), 135.2 (Ar$\underline{C}$-quat), 156.6 (CO), 166.9 (CO), 171.0 (CO, rotamer at 171.2); ***m/z* (ES$^+$)** 449 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 449.2173 for $C_{23}H_{30}N_4O_4Na^+$ [M+Na]$^+$, requires 449.2170.

7.2.5.3 Synthesis and characterisation of 4-methyl-N-(2-{2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)benzene sulfonamide (**2.59**)



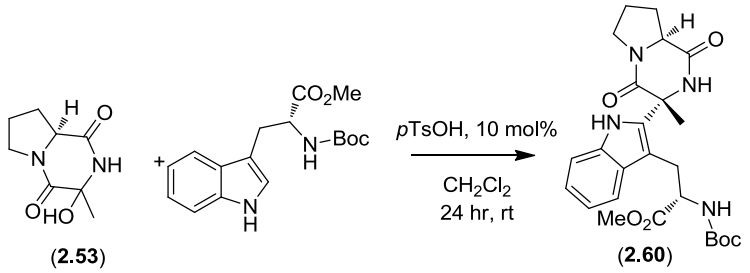
(**2.53**) (**2.59**)

Following the general procedure (0.58 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 8) was obtained after 24 hours at room temperature as a colourless solid

following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (267 mg, 96%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 144-148 ºC; **$[\alpha]_D^{24}$** = - 42.3 (c = 1.27 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3284 (br m, N-H), 1680 (s, C=O), 1659 (s, C=O), 1325 (br m, S=O), 1157 (s, S-O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.62-1.73 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.80 (s, 3H, $C\underline{H}_3$), 1.86-1.93 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.01-2.10 (m, 1H, $NCHC\underline{H}_AH_B$), 2.16-2.22 (m, 1H, $NCHCH_A\underline{H}_B$), 2.26 (s, 3H, $C\underline{H}_3$), 2.91-2.98 (m, 1H, $NCH_2C\underline{H}_AH_BC$), 3.02-3.14 (m, 3H, $NCH_2CH_A\underline{H}_BC$, $NC\underline{H}_2CH_2C$), 3.39 (ddd, 1H, *J* = 11.7 Hz, *J* = 8.8 Hz, *J* = 2.7 Hz, $NC\underline{H}_AH_BCH_2CH_2$), 3.48-3.55 (m, 1H, $NCH_AH_BCH_2CH_2$), 3.85 (dd, 1H, *J* = 9.4 Hz, *J* = 7.4 Hz, $NC\underline{H}CH_2$), 5.63 (t, 1H, *J* = 5.7 Hz, $N\underline{H}CH_2$), 6.96 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.04-7.08 (m, 3H, Ar-H indole, 2 x Ar-H), 7.22 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.30 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 7.50 (d, 2H, *J* = 8.3 Hz, 2 x Ar-H), 8.15 (br s, 1H, N-H), 9.13 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 21.8 ($\underline{C}H_3$), 22.9 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 26.6 ($\underline{C}H_3$), 28.3 ($\underline{C}H_2$), 43.9 ($N\underline{C}H_2CH_2C$), 46.4 ($N\underline{C}H_2CH_2CH_2$), 59.1 ($N\underline{C}HCH_2$), 61.0 ($CH_3\underline{C}$), 108.9 (Ar$\underline{C}$-quat), 111.6 (Ar$\underline{C}$-H indole), 118.7 (Ar$\underline{C}$-H indole), 120.1 (Ar$\underline{C}$-H indole), 123.0 (Ar$\underline{C}$-H indole), 127.3 (2 x Ar$\underline{C}$-H), 128.7 (Ar$\underline{C}$-quat), 129.8 (2 x Ar$\underline{C}$-H), 132.7 (Ar$\underline{C}$-quat), 135.5 (Ar$\underline{C}$-quat), 136.9 (Ar$\underline{C}$-quat), 143.4 (Ar$\underline{C}$-quat), 167.1 (CO), 171.8 (CO); ***m/z* (ES$^+$)** 503 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 503.1731 for $C_{25}H_{28}N_4O_4SNa^+$ [M+Na]$^+$, requires 503.1734.

7.2.5.4 Synthesis and characterisation of methyl *N*-(*tert*-butoxycarbonyl)-2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-L-tryptophanate (**2.60**)



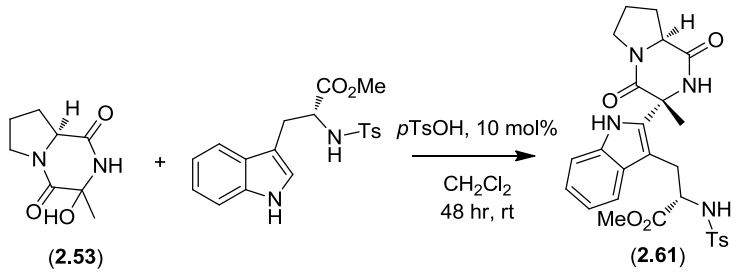
(**2.53**) (**2.60**)

Following the general procedure (0.38 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 19) was obtained after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) as a mixture of rotamers (1 : 1.8) (165 mg, 90%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 141-144 ºC; **$[\alpha]_D^{24}$** = - 13.4 (c = 2.15 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3320 (br w, N-H), 1745 (s, C=O), 1669 (br s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.30 (s, 9H, $C(C\underline{H}_3)_3$, rotamer at 0.76 ppm), 1.69-1.80 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.91 (s, 3H, $C\underline{H}_3C$, rotamer at 1.92 ppm), 1.93-1.96 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.07-2.16 (m, 1H, $NCHC\underline{H}_AH_B$), 2.25-2.32 (m, 1H, $NCHCH_A\underline{H}_B$), 3.13-3.22 (m, 2H, $NHCHC\underline{H}_2C$), 3.49 (s, 3H, $OC\underline{H}_3$, rotamer at 3.67 ppm), 3.51-3.64 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 3.93-4.01 (m, 1H, $NC\underline{H}CH_2$), 4.43 (dd, 1H, *J* = 15.2 Hz, *J* = 7.9 Hz, $NHC\underline{H}CH_2C$, rotamer at 4.61 ppm), 6.07 (d, 1H, *J* = 8.1 Hz, $N\underline{H}CHCH_2C$, rotamer at 6.41 ppm), 7.02-7.17 (m, 2H, 2 x Ar-H), 7.24-7.31 (m, 1H, Ar-H), 7.45 (d, 1H, *J* = 7.8 Hz, Ar-H, rotamer at 7.54 ppm), 8.80-8.84 (m, 2H, 2 x N-H, rotamer at 9.14 ppm); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.6 ($NCH_2\underline{C}H_2CH_2$), 26.7 ($\underline{C}H_3C$), 26.8 &

27.1 & 27.4 & 28.0 & 28.1 & 28.4 (NCH$\underline{C}$H$_2$, NHCH$\underline{C}$H$_2$C, C($\underline{C}$H$_3$)$_3$, 3 x rotamers), 46.1 (N$\underline{C}$H$_2$CH$_2$CH$_2$), 52.3 ($CO_2\underline{C}H_3$), 55.1 (NH$\underline{C}$HCH$_2$C, rotamer at 54.9 ppm), 58.6 (N$\underline{C}$HCH$_2$), 61.0 (C-quat, rotamer at 61.2 ppm), 79.9 (C-quat, rotamer at 79.5 ppm), 108.0 (Ar$\underline{C}$-quat, rotamer at 107.8 ppm), 111.2 (Ar$\underline{C}$-H, rotamer at 111.3 ppm), 118.4 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 122.7 (Ar$\underline{C}$-H), 128.7 (Ar$\underline{C}$-quat), 132.5 (Ar$\underline{C}$-quat, rotamer at 132.9 ppm), 135.6 (Ar$\underline{C}$-quat, rotamer at 135.2 ppm), 155.9 (CO, rotamer at 155.0 ppm), 167.0 (CO), 171.7 (CO, rotamer at 171.2 ppm), 173.4 (CO, rotamer at 173.1 ppm); ***m/z* (ES$^+$)** 507 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 507.2222 for $C_{25}H_{32}N_4O_6Na^+$ [M+Na]$^+$, requires 507.2225.

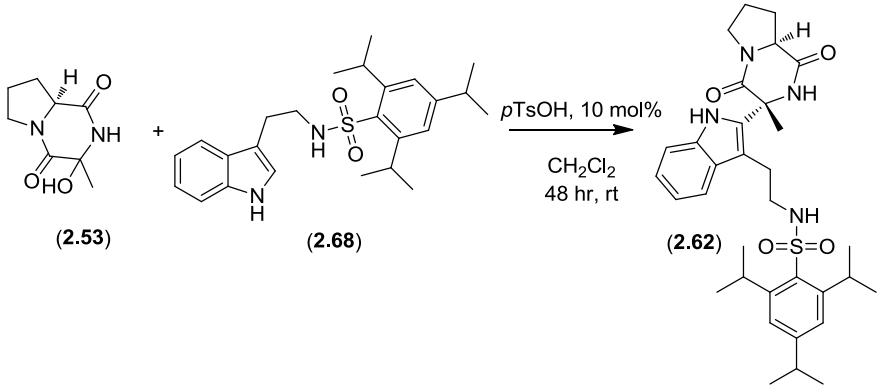
7.2.5.5 Synthesis and characterisation of methyl 2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-*N*-[(4-methylphenyl)sulfonyl]-L-tryptophanate (**2.61**)



Following the general procedure (0.62 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 18) was obtained after 48 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (177 mg, 53%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 132-134 **º**C; **[α]$_D^{24}$** = - 50.2 (c = 2.21 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3232 (br m, N-H), 1747 (m, C=O), 1669 (br s, C=O) 1341 (br m, S=O), 1158 (s, S-O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.73-1.83 (m, 4H, C$\underline{H}_3$C, NCH$_2$C$\underline{H}_A$H$_B$CH$_2$), 1.94-2.02 (m, 1H, NCH$_2$CH$_A\underline{H}_B$CH$_2$), 2.08-2.17 (m, 4H, C$\underline{H}_3$, NCHC$\underline{H}_A$H$_B$), 2.46-2.53 (m, 1H, NCHCH$_A\underline{H}_B$), 2.95-3.09 (m, 2H, NHCHC$\underline{H}_2$C), 3.46-3.60 (m, 2H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.63 (s, 3H, $CO_2C\underline{H}_3$), 4.11-4.17 (m, 2H, NC$\underline{H}$CH$_2$, NHC$\underline{H}$CH$_2$C), 6.62 (d, 2H, *J* = 8.1 Hz, 2 x Ar-H), 6.97 (d, 2H, *J* = 8.2 Hz, 2 x Ar-H), 7.00 (d, 1H, *J* = 7.4 Hz, Ar-H indole), 7.08-7.13 (m, 1H, Ar-H indole), 7.16-7.20 (m, 1H, Ar-H indole), 7.24 (br d, 1H, *J* = 10.5 Hz, N-H) 7.31 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 8.62 (br s, 1H, N-H), 9.46 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 21.4 ($\underline{C}H_3$C), 22.6 (NCH$_2\underline{C}$H$_2$CH$_2$), 27.4 & 27.5 & 28.0 (NHCH$\underline{C}$H$_2$C, NCH$\underline{C}$H$_2$, $\underline{C}$H$_3$), 46.2 (N$\underline{C}$H$_2$CH$_2$CH$_2$), 52.6 ($CO_2\underline{C}H_3$), 56.1 & 58.6 (NH$\underline{C}$HCH$_2$C, N$\underline{C}$HCH$_2$), 61.0 (CH$_3\underline{C}$), 106.9 (Ar$\underline{C}$-quat), 111.2 (Ar$\underline{C}$-H indole), 117.8 (Ar$\underline{C}$-H indole), 120.0 (Ar$\underline{C}$-H indole), 122.8 (Ar$\underline{C}$-H indole), 126.1 (2 x Ar$\underline{C}$-H), 127.5 (Ar$\underline{C}$-quat), 128.7 (2 x Ar$\underline{C}$-H), 132.2 (Ar$\underline{C}$-quat), 135.4 (Ar$\underline{C}$-quat), 136.6 (Ar$\underline{C}$-quat), 142.5 (Ar$\underline{C}$-quat), 166.3 (CO), 173.0 (CO); ***m/z* (ES$^+$)** 561 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 561.1785 for $C_{27}H_{30}N_4O_6SNa^+$ [M+Na]$^+$, requires 561.1789.

7.2.5.6 Synthesis and characterisation of 2,4,6-triisopropyl-*N*-(2-{2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)benzenesulfonamide (**2.62**)

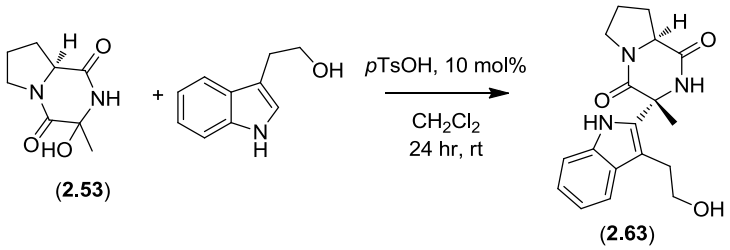


(**2.53**) (**2.68**) (**2.62**)

Following the general procedure (0.54 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 17) was obtained after 48 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (225 mg, 70%). The dr was determined by analysis of the crude ^{1}H NMR. The major diastereomer was recrystalised (EtOAc/petroleum ether) and the absolute stereochemistry was proved by X-ray analysis.

M.P. 132-134 ºC; **$[\alpha]_D^{24}$** = - 39.8 (c = 1.91 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3299 (br m, N-H), 1675 (br s, C=O), 1313 (br m, S=O), 1149 (br s, S-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.12 (d, 6H, *J* = 6.8 Hz, $CH(C\underline{H}_3)_2$), 1.15-1.19 (m, 12H, 2 x $CH(C\underline{H}_3)_2$), 1.65-1.76 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.87 (s, 3H, $C\underline{H}_3C$), 1.89-1.96 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.01-2.11 (m, 1H, $NCHC\underline{H}_AH_B$), 2.18-2.25 (m, 1H, $NCHCH_A\underline{H}_B$), 2.82 (sept., 1H, *J* = 6.8 Hz, $(CH_3)_2C\underline{H}CCHCCSO_2$), 2.92-2.98 (m, 1H, $NHCH_2C\underline{H}_AH_BC$), 3.05-3.16 (m, 2H, $NHC\underline{H}_2CH_2C$), 3.25-3.34 (m, 1H, $NHCH_2CH_A\underline{H}_BC$), 3.41 (ddd, 1H, *J* = 11.9 Hz, *J* = 8.9 Hz, *J* = 3.1 Hz, $NC\underline{H}_AH_BCH_2CH_2$), 3.51-3.58 (m, 1H, $NCH_A\underline{H}_BCH_2CH_2$), 3.80-3.84 (m, 1H, $NC\underline{H}CH_2$), 3.99-4.05 (m, 2H, 2 x $(CH_3)_2C\underline{H}CCSO_2$), 4.79 (t, 1H, *J* = 6.0 Hz, $N\underline{H}CH_2$), 6.98-7.02 (m, 1H, Ar-H indole), 7.08 (s, 2H, 2 x Ar-H), 7.10-7.14 (m, 1H, Ar-H indole), 7.24 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.32 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 7.82 (br s, 1H, N-H), 8.81 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 22.6 ($NCH_2\underline{C}H_2CH_2$), 23.6 ($CH(\underline{C}H_3)_2$), 24.4 ($NHCH_2\underline{C}H_2C$), 24.8 ($CH(\underline{C}H_3)_2$), 24.9 ($CH(\underline{C}H_3)_2$), 26.5 ($\underline{C}H_3C$), 28.1 ($NCH\underline{C}H_2$), 29.6 (2 x $(CH_3)_2\underline{C}HCCSO_2$), 34.1 ($(CH_3)_2\underline{C}HCCHCCSO_2$), 43.2 ($NH\underline{C}H_2CH_2C$), 46.0 ($N\underline{C}H_2CH_2CH_2$), 58.8 ($\underline{C}HCH_2$), 60.7 ($CH_3\underline{C}$), 108.6 (Ar$\underline{C}$-quat), 111.3 (Ar$\underline{C}$-H indole), 118.4 (Ar$\underline{C}$-H indole), 119.9 (2 x Ar$\underline{C}$-H indole), 122.8 (Ar$\underline{C}$-quat), 123.8 (2 x Ar$\underline{C}$-H) , 128.4 (Ar$\underline{C}$-quat), 131.8 (Ar$\underline{C}$-quat) 132.7 (Ar$\underline{C}$-quat), 135.2 (Ar$\underline{C}$-quat), 150.5 (Ar$\underline{C}$-quat), 152.7 (Ar$\underline{C}$-quat), 166.7 (CO), 171.1 (CO); ***m/z* (ES$^+$)** 615 ($[M+Na]^+$, 100%); **HRMS ES (+)** Found 615.2975 for $C_{33}H_{44}N_4O_4SNa^+$ $[M+Na]^+$, requires 615.2986.

7.2.5.7 Synthesis and characterisation of (3*R*,8a*S*)-3-[3-(2-hydroxyethyl)-1*H*-indol-2-yl]-3-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.63**)

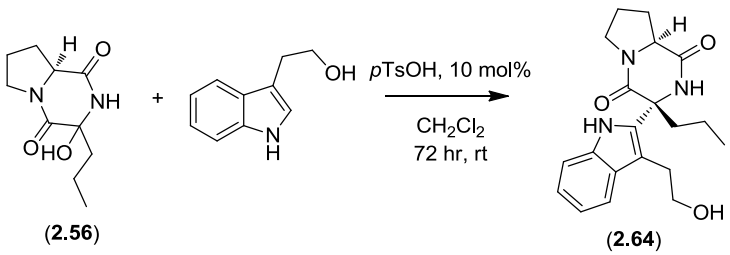


(**2.53**) (**2.63**)

Following the general procedure (2.88 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 14) was obtained after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (902 mg, 96%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 75-77 ºC; **$[\alpha]_D^{24}$** = - 75.0 (c = 1.39 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3300 (br w, N-H, O-H), 1659 (br s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.71-1.79 (m, 1H, $NCH_2C\underline{H}_AH_BCH_2$), 1.84 (s, 3H, $C\underline{H}_3C$), 1.93-2.08 (m, 2H, $NCH_2CH_A\underline{H}_BCH_2$, $NCHC\underline{H}_AH_B$), 2.25-2.31 (m, 1H, $NCHCH_A\underline{H}_B$), 2.99 (app. dt, 1H, *J* = 15.0 Hz, *J* = 4.4 Hz, $OCH_2C\underline{H}_AH_B$), 3.11 (ddd, 1H, *J* = 15.0 Hz, *J* = 9.7 Hz *J* = 4.4 Hz, $OCH_2CH_A\underline{H}_B$), 3.45 (ddd, 1H, *J* = 12.1 Hz, *J* = 9.1 Hz, *J* = 2.9 Hz, $NC\underline{H}_AH_BCH_2CH_2$), 3.57-3.63 (m, 1H, $NCH_A\underline{H}_BCH_2CH_2$), 3.70 (app. dt, 1H, *J* = 9.7 Hz, *J* = 3.8 Hz, $OC\underline{H}_AH_BCH_2$), 3.87 (dd, 1H, *J* = 10.0 Hz, *J* = 6.9 Hz, $NC\underline{H}CH_2$), 3.97 (app. dt, 1H, *J* = 9.7 Hz, *J* = 4.4 Hz, $OCH_A\underline{H}_BCH_2$), 7.03-7.07 (m, 1H, Ar-H), 7.12-7.16 (m, 1H, Ar-H), 7.25 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.44 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.54 (br s, 1H, N-H), 8.56 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, $CDCl_3$) 22.7 ($\underline{C}H_2$), 26.9 ($\underline{C}H_2$), 27.5 ($\underline{C}H_3$), 28.6 ($\underline{C}H_2$), 46.2 ($N\underline{C}H_2CH_2$), 59.1 ($N\underline{C}HCH_2$), 61.1 ($CH_3\underline{C}$), 63.3 ($O\underline{C}H_2CH_2$), 109.5 (Ar$\underline{C}$-quat), 111.4 (Ar$\underline{C}$-H), 118.7 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 123.0 (Ar$\underline{C}$-H), 128.9 (Ar$\underline{C}$-quat), 133.0 (Ar$\underline{C}$-quat), 135.6 (Ar$\underline{C}$-quat), 167.1 (CO), 171.1 (CO); ***m/z* (ES$^-$)** 326 ([M-H], 100%); **HRMS ES (+)** Found 350.1478 for $C_{18}H_{21}N_3O_3Na^+$ $[M+Na]^+$, requires 350.1475.

7.2.5.8 Synthesis and characterisation of (3*R*,8a*S*)-3-[3-(2-hydroxyethyl)-1*H*-indol-2-yl]-3-propylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2.64**)



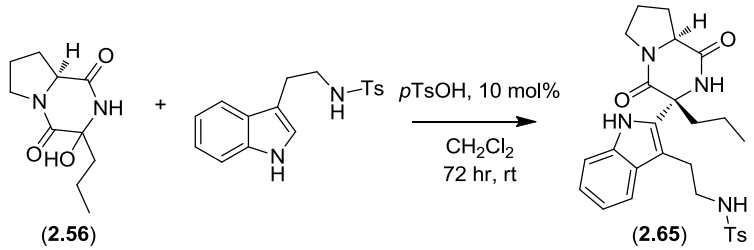
(**2.56**) (**2.64**)

Following the general procedure (0.54 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 11) was obtained after 72 hours at room temperature as a colourless solid

following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (165 mg, 86%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 80-85 ºC; **$[\alpha]_D^{25}$** = - 64.3 (c = 1.25 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3273 (br w, N-H, O-H), 1660 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.85 (t, 3H, *J* = 7.3 Hz, C$\underline{H}_3$CH$_2$CH$_2$), 1.26-1.38 (m, 2H, CH$_3$C$\underline{H}_2$CH$_2$), 1.67-1.79 (m, 1H, NCH$_2$C$\underline{H}_A$H$_B$CH$_2$), 1.83-2.04 (m, 3H, NCH$_2$CH$_A$$\underline{H}_BCH_2$, NCHC$\underline{H}_AH_B$, CH$_3CH_2C\underline{H}_AH_B$), 2.24-2.41 (m, 2H, NCHCH$_A$$\underline{H}_B$, CH$_3CH_2CH_A$$\underline{H}_B$), 2.64 (br s, 1H, O-H), 2.99-3.14 (m, 2H, OCH$_2$C$\underline{H}_2$C), 3.43 (ddd, 1H, *J* = 11.9 Hz, *J* = 9.3 Hz, *J* = 2.5 Hz, NC$\underline{H}_A$H$_B$CH$_2$CH$_2$), 3.56-3.65 (m, 1H, NCH$_A$$\underline{H}_BCH_2CH_2$), 3.67-3.74 (m, 1H, OC$\underline{H}_AH_BCH_2$C), 3.85-3.93 (m, 2H, OCH$_A$$\underline{H}_BCH_2C, NC\underline{H}CH_2$), 7.01-7.05 (m, 1H, Ar-H), 7.09-7.14 (m, 1H, Ar-H), 7.24 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.45 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.01 (br s, 1H, N-H), 8.78 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.0 (C$\underline{H}_3$CH$_2$CH$_2$), 17.6 (CH$_3$C$\underline{H}_2$CH$_2$), 22.2 (NCH$_2$C$\underline{H}_2$CH$_2$), 26.8 (OCH$_2$C$\underline{H}_2$C), 28.6 (CH$_3$CH$_2$C$\underline{H}_2$), 42.5 (NCHC$\underline{H}_2$CH$_2$), 45.7 (NC$\underline{H}_2$CH$_2$CH$_2$), 58.6 (NC$\underline{H}$CH$_2$), 63.1 (OC$\underline{H}_2$CH$_2$C), 64.4 (CH$_2$C), 109.4 (ArC-quat), 111.0 (ArC-H), 118.4 (ArC-H), 119.6 (ArC-H), 122.7 (ArC-H), 128.6 (ArC-quat), 132.3 (ArC-quat), 135.3 (ArC-quat), 165.9 (CO), 170.5 (CO); ***m/z* (ES$^+$)** 378 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 378.1781 for $C_{20}H_{25}N_3O_3Na^+$ [M+Na]$^+$, requires 378.1788.

7.2.5.9 Synthesis and characterisation of *N*-(2-{2-[(3*R*,8a*S*)-1,4-dioxo-3-propyloctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)-4-methylbenzenesulfonamide (**2.65**)

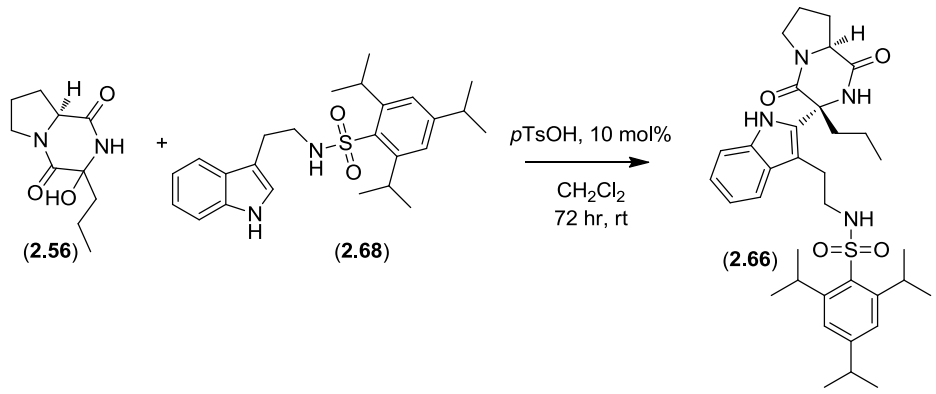


Following the general procedure (0.45 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 9) was obtained after 72 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (141 mg, 51%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 110-115 ºC; **$[\alpha]_D^{25}$** = - 30.6 (c = 0.66 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3284 (br w, N-H), 1656 (s, C=O), 1618 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.84 (t, 3H, *J* = 7.3 Hz, C$\underline{H}_3$CH$_2$CH$_2$), 1.17-1.27 (m, 1H, CH$_3$C$\underline{H}_A$H$_B$) , 1.30-1.41 (m, 1H, CH$_3$CH$_A$$\underline{H}_B$), 1.65-1.75 (m, 1H, NCH$_2C\underline{H}_AH_BCH_2$), 1.88-1.96 (m, 1H, NCH$_2CH_A$$\underline{H}_BCH_2$), 1.97-2.07 (m, 2H, NCHC$\underline{H}_A$H$_B$, CH$_3$CH$_2$C$\underline{H}_A$H$_B$), 2.20-2.27 (m, 2H, NCHCH$_A$$\underline{H}_B$, CH$_3CH_2CH_A$$\underline{H}_B$), 2.30 (s, 3H, C$\underline{H}_3$CCH), 2.95-3.01 (m, 1H, NHCH$_2$C$\underline{H}_A$H$_B$C), 3.06-3.17 (m, 3H, NHCH$_2$CH$_A$$\underline{H}_BC, NC\underline{H}_2CH_2$C), 3.41 (ddd, 1H, *J* = 11.8 Hz, *J* = 9.1 Hz, *J* = 2.6 Hz, NC$\underline{H}_A$H$_B$CH$_2$CH$_2$), 3.50-3.56 (m, 1H, NCH$_A$$\underline{H}_BCH_2CH_2$), 3.85 (dd, 1H, *J* = 9.8 Hz, *J* = 7.1 Hz, NC$\underline{H}$CH$_2$), 5.35 (t, 1H, *J* = 5.9 Hz, N$\underline{H}$CH$_2$), 6.99 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.07-7.13 (m, 3H, Ar-H indole, 2 x Ar-H), 7.22 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.33 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 7.56 (d, 2H, *J* = 8.1 Hz, 2 x Ar-H), 7.86 (br s, 1H, N-H), 8.81 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.0 (C$\underline{H}_3$CH$_2$CH$_2$), 17.5 (CH$_3$C$\underline{H}_2$CH$_2$), 21.5 (C$\underline{H}_3$CCH), 22.4 (NCH$_2$C$\underline{H}_2$CH$_2$), 24.5 (NHCH$_2$C$\underline{H}_2$C), 28.2 (C$\underline{H}_2$), 41.2 (C$\underline{H}_2$), 43.8 (NHC$\underline{H}_2$CH$_2$C), 45.9 (NC$\underline{H}_2$CH$_2$CH$_2$), 58.5 (NC$\underline{H}$CH$_2$),

64.3 (CH_2C), 109.0 (ArC-quat), 111.2 (ArC-H indole), 118.5 (ArC-H indole), 119.8 (ArC-H indole), 122.7 (ArC-H indole), 127.1 (2 x ArC-H), 128.6 (ArC-quat), 129.5 (2 x ArC-H), 131.6 (ArC-quat), 135.1 (ArC-quat), 136.7 (ArC-quat), 143.2 (ArC-quat), 165.9 (CO), 171.5 (CO); ***m/z* (ES$^+$)** 531 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 531.2060 for $C_{27}H_{32}N_4O_4SNa^+$ [M+Na]$^+$, requires 531.2036.

7.2.5.10 Synthesis and characterisation of *N*-(2-{2-[(3*R*,8a*S*)-1,4-dioxo-3-propyloctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)-2,4,6-triisopropylbenzenesulfonamide (**2.66**)



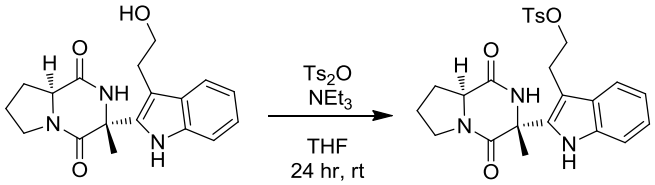
Following the general procedure (0.43 mmol scale) the titled compound (as a mixtures of diastereomers (1 : 9) was obtained after 72 hours at room temperature as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (73 mg, 37%). The dr was determined by analysis of the crude ^{1}H NMR.

M.P. 132-134 **ºC**; **$[\alpha]_D^{25}$** = - 14.3 (c = 1.35 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3270 (br w, N-H), 1657 (br s, C=O), 1316 (br w, S=O), 1149 (s, S-O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 0.83 (t, 3H, *J* = 7.3 Hz, CH_3CH_2), 1.11 (d, 6H, *J* = 6.7 Hz, $(CH_3)_2CH$), 1.14-1.18 (m, 12H, 2 x $(CH_3)_2CH$), 1.21-1.30 (m, 1H, CHH), 1.33-1.42 (m, 1H, CHH), 1.64-1.74 (m, 1H, CHH), 1.86-1.94 (m, 1H, CHH), 1.98-2.12 (m, 2H, 2 x CHH), 2.16-2.30 (m, 2H, 2 x CHH), 2.81 (sept., 1H, *J* = 6.9 Hz, $(CH_3)_2CHCCHCCSO_2$) 2.98-3.04 (m, 1H, $NHCH_2CH_AH_BC$), 3.06-3.13 (m, 2H, $NHCH_2CH_2C$), 3.17-3.23 (m, 1H, $NHCH_2CH_AH_BC$), 3.37-3.42 (m, 1H, $NCH_AH_BCH_2CH_2$), 3.50-3.57 (m, 1H, $NCH_AH_BCH_2CH_2$), 3.82 (dd, 1H, *J* = 9.4 Hz, *J* = 7.3 Hz, $NCHCH_2$), 4.02-4.10 (m, 2H, 2 x $(CH_3)_2CHCCSO_2$), 5.15 (t, 1H, *J* = 6.0 Hz, $NHCH_2$), 6.96 (t, 1H, *J* = 7.5 Hz, Ar-H indole), 7.05-7.09 (m, 3H, Ar-H indole, 2 x Ar-H), 7.23 (d, 1H, *J* = 8.1 Hz, Ar-H indole), 7.29 (d, 1H, *J* = 7.9 Hz, Ar-H indole), 7.84 (br s, 1H, N-H), 8.90 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, $CDCl_3$) 14.2 ($CH_3CH_2CH_2$), 17.8 ($(CH_3)_2CH$), 22.7 (CH_2), 23.9 (CH_2), 24.9 (CH_2), 25.1 ($(CH_3)_2CH$), 25.2 ($(CH_3)_2CH$), 28.4 (CH_2), 29.9 (2 x $(CH_3)_2CHCCSO_2$), 34.4 ($(CH_3)_2CHCCHCCSO_2$), 41.5 (CH_2), 43.6 ($NHCH_2CH_2C$), 46.1 ($NCH_2CH_2CH_2$), 58.8 ($NCHCH_2$), 64.5 (CH_2C), 109.2 (ArC-quat), 111.5 (ArC-H indole),118.7 (ArC-H indole), 120.1 (ArC-H indole), 123.0 (ArC-H indole), 124.0 (2 x ArC-H), 128.9 (ArC-quat), 132.2 (ArC-quat), 132.2 (ArC-quat), 135.4 (ArC-quat), 150.8 (2 x ArC-quat), 153.0 (ArC-quat), 166.2 (CO), 171.5 (CO); ***m/z* (ES$^+$)** 643 ([M+Na]$^+$, 100%); **HRMS ES (+)** Found 643.3302 for $C_{35}H_{48}N_4O_4SNa^+$ [M+Na]$^+$, requires 643.3288.

7.3 Experimental for chapter 3

7.3.1 Synthesis of the fused pentacycle

7.3.1 Synthesis and characterisation of 4-methyl-*N*-(2-{2-[(3*R*,8a*S*)-3-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]-1*H*-indol-3-yl}ethyl)benzenesulfonamide (**3.36**)

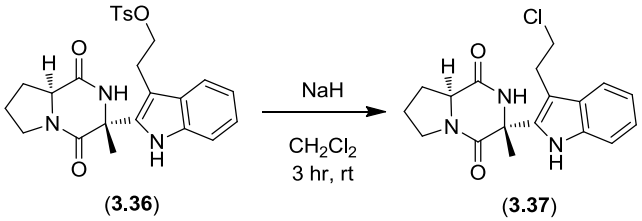


(**2.63**) (**3.36**)

To a solution of primary alcohol (**2.63**) (562 mg, 1.72 mmol) in THF (3 mL), was added NEt_3 (263 µL,1.89 mmol) and Ts_2O (616 mg, 1.89 mmol) and the solution was stirred at room temperature for 24 hours before evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate : petroleum ether, 3 : 1) afforded the titled compound as a colourless solid (674 mg, 82%).

M.P. 120-122 **ºC**; **$[\alpha]_D^{25}$** = - 52.3 (c = 1.19 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3263 (br w, N-H), 1675 (s, C=O), 1659 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.71-1.79 (m, 1H, $NCHCH_2C\underline{H}_A\underline{H}_B$), 1.82 (s, 3H, $C\underline{H}_3$), 1.89-1.96 (m, 1H, $NCHCH_2CH_A\underline{H}_B$), 2.04-2.13 (m, 1H, $NCHC\underline{H}_A\underline{H}_B$), 2.20-2.26 (m, 1H, $NCHCH_A\underline{H}_B$), 2.28 (s, 3H, $C\underline{H}_3$), 3.12 (app. dt, 1H, *J* = 14.9 Hz, *J* = 5.9 Hz, $S(O)_2OCH_2C\underline{H}_A\underline{H}_B$), 3.22-3.29 (m, 1H, $S(O)_2OCH_2CH_A\underline{H}_B$), 3.43 (ddd, 1H, *J* = 11.9 Hz, *J* = 8.8 Hz, *J* = 3.2 Hz, $NC\underline{H}_A\underline{H}_BCH_2$), 3.54-3.61 (m, 1H, $NCH_A\underline{H}_BCH_2$), 3.87 (dd, 1H, *J* = 9.5 Hz, *J* = 7.3 Hz, $NC\underline{H}CH_2$), 4.03-4.09 (m, 1H, $S(O)_2OC\underline{H}_A\underline{H}_B$), 4.17 (app. dt, 1H, *J* = 9.5 Hz, *J* = 5.9 Hz, $S(O)_2OCH_A\underline{H}_B$), 6.96 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.05-7.12 (m, 3H, 3 x Ar-H), 7.23 (d, 2H, *J* = 8.8 Hz, 2 x Ar-H), 7.41 (s, 1H, N-H amide), 7.50 (d, 2H, *J* = 8.3 Hz, 2 x Ar-H), 8.85 (s, 1H, N-H indole); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 21.6 ($\underline{C}H_3$), 22.6 ($NCHCH_2\underline{C}H_2$), 23.6 ($S(O)_2OCH_2\underline{C}H_2$), 26.7 ($\underline{C}H_3$), 28.1 ($NCH\underline{C}H_2$), 46.1 ($N\underline{C}H_2CH_2$), 58.7 ($N\underline{C}HCH_2$), 60.8 ($CH_3\underline{C}$), 69.9 ($S(O)_2O\underline{C}H_2CH_2$), 106.7 (Ar$\underline{C}$-quat), 111.2 (Ar$\underline{C}$-H), 118.2 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 122.8 (Ar$\underline{C}$-H), 126.1 (Ar$\underline{C}$-H), 127.8 (Ar$\underline{C}$-H), 128.2 (Ar$\underline{C}$-quat), 129.3 (Ar$\underline{C}$-H), 129.7 (Ar$\underline{C}$-H), 132.2 (Ar$\underline{C}$-quat), 132.8 (Ar$\underline{C}$-quat), 135.2 (Ar$\underline{C}$-quat), 144.7 (Ar$\underline{C}$-quat), 166.3 (CO), 171.2 (CO); ***m/z* (ES$^+$)** 504 ($[M+Na]^+$, 100%); **HRMS ES (+)** Found 504.1562 for $C_{25}H_{27}O_5N_3SNa^+$ $[M+Na]^+$, requires 504.1564.

7.3.1.2 Synthesis and characterisation of (3*R*,8a*S*)-3-[3-(2-chloroethyl)-1*H*-indol-2-yl]-3-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**3.37**)

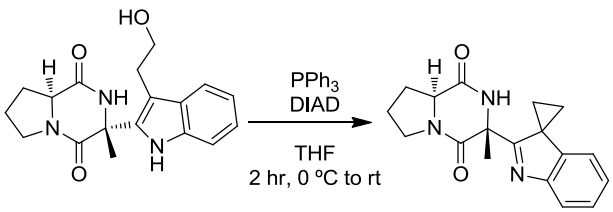


(**3.36**) (**3.37**)

To a suspension of NaH (4.8 mg, 0.20 mmol), in CH_2Cl_2 (1 mL), under N_2 was added a solution of tosylate (**3.36**) (47 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature for 3 hours before the addition of 1 M aqueous HCl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the crude. Purification of the crude by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate : petroleum ether, 3 : 1) afforded the titled compound as a pale yellow solid (24 mg, 72%)

M.P. 220-124 **º**C; **$[\alpha]_D^{25}$** = - 57.0 (c = 1.22 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3275 (br w, N-H), 1677 (s, C=O), 1659 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.69-1.80 (m, 1H, $NCH_2CH_AH_B$), 1.87 (s, 3H, CH_3), 1.92-2.00 (m, 1H, $NCH_2CH_AH_B$), 2.03-2.13 (m, 1H, $NCHCH_AH_B$), 2.21-2.27 (m, 1H, $NCHCH_AH_B$), 3.30 (dd, 2H, *J* = 7.4 Hz, *J* = 6.5 Hz, $ClCH_2CH_2$), 3.46 (ddd, 1H, *J* = 11.9 Hz, *J* = 8.9 Hz, *J* = 3.0 Hz, $NCH_AH_BCH_2$), 3.55-3.67 (m, 2H, $NCH_AH_BCH_2$, $ClCH_AH_BCH_2$), 3.76 (dt, 1H, *J* = 10.6 Hz, *J* = 6.5 Hz, $ClCH_AH_BCH_2$), 3.87 (dd, 1H, *J* = 9.6 Hz, *J* = 7.2 Hz, $NCHCH_2$), 7.07 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.16 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.25 (d, 1H, *J* = 6.9 Hz, Ar-H), 7.28 (br s, 1H, N-H), 7.46 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.65 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.6 (NCH_2CH_2), 27.8 ($ClCH_2CH_2$), 27.2 (CH_3), 28.1 ($NCHCH_2$), 45.2 ($ClCH_2CH_2$), 46.0 (NCH_2CH_2), 58.8 ($NCHCH_2$), 60.9 (CH_3C), 108.7 (ArC-quat), 111.2 (ArC-H), 118.3 (ArC-H), 120.0 (ArC-H),123.0 (ArC-H), 128.4 (ArC-quat), 132.6 (ArC-quat), 135.2 (ArC-quat), 166.3 (CO), 170.6 (CO); ***m/z* (ES$^-$)** 344 ([M-H]$^-$, 55%), 689 ([2M-H]$^-$, 100%); **HRMS ES (+)** Found 368.1136 for $C_{18}H_{20}N_3O_2{}^{35}ClNa^+$ $[M+Na]^+$, requires 368.1136.

7.3.1.3 Synthesis and characterisation of (3*R*,8a*S*)-3-methyl-3-(spiro[cyclopropane-1,3'-indol]-2'-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**3.39**)



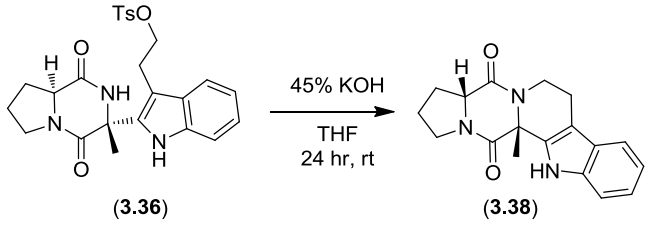
(**2.63**) (**3.39**)

To a solution of primary alcohol (**2.63**) (143 mg, 0.44 mmol) in THF (6 mL) under N_2, was added PPh_3 (172 mg, 0.66 mmol) and the solution was cooled to 0 ºC before the addition of DIAD (0.13

mL, 0.66 mmol). The solution was allowed to warm to room temperature where it was stirred for 2 hours before evaporating the solvent *in vacuo* to afford the crude. Purification of the crude by flash silica gel chromatography (increasing polarity from diethyl ether to diethyl ether : methanol, 9.5 : 0.5) afforded the titled compound as a colourless solid (78 mg, 58%).

M.P. 77-80 **ºC**; **$[\alpha]_D^{25}$** = - 7.0 (c = 1.4 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3249 (br w, N-H), 1725 (s, CO), 1674 (s, CO); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.60-1.65 (m, 1H, C<u>H</u>H), 1.66 (s, 3H, C<u>H</u>$_3$), 1.69-1.80 (m, 2H, 2 x C<u>H</u>H), 1.89-1.96 (m, 1H, C<u>H</u>H), 2.00-2.08 (m, 1H, C<u>H</u>H), 2.24-2.33 (m, 3H, 3 x C<u>H</u>H), 3.42 (ddd, 1H, *J* = 11.8 Hz, *J* = 8.8 Hz, *J* = 2.9 Hz, NC<u>H</u>$_A$H$_B$CH$_2$), 3.53-3.60 (m, 1H, NCH$_A$<u>H</u>$_B$CH$_2$), 3.99 (dd, 1H, *J* = 9.7 Hz, *J* = 7.2 Hz, NC<u>H</u>CH$_2$), 6.32 (br s, 1H, N-H), 6.91 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.23 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.32 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.68 (d, 1H, *J* = 7.7 Hz, Ar-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 19.4 (<u>C</u>H$_2$), 20.5 (<u>C</u>H$_2$), 22.7 (<u>C</u>H$_2$), 23.2 (<u>C</u>H$_3$), 28.5 (<u>C</u>H$_2$), 35.7 (C-quat), 46.1 (N<u>C</u>H$_2$CH$_2$), 59.4 (N<u>C</u>HCH$_2$), 63.2 (C-quat), 116.9 (Ar<u>C</u>-H), 121.3 (Ar<u>C</u>-H), 125.7 (Ar<u>C</u>-H), 126.7 (Ar<u>C</u>-H), 142.5 (Ar<u>C</u>-quat), 151.8 (Ar<u>C</u>-quat), 164.7 (Ar<u>C</u>-quat), 171.9 (CO), 178.2 (CO); ***m/z* (ES$^+$)** 332 ([M+Na]$^+$, 30%), 641 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 332.1369 for $C_{18}H_{19}N_3O_2Na^+$ [M+Na]$^+$, requires 332.1369.

7.3.1.4 Synthesis and characterisation of (3a*R*,12b*R*)-12b-methyl-1,2,3,3a,6,7,12,12b-octahydro-4*H*,13*H*-pyrrolo[1'',2'':4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indole-4,13-dione (**3.38**)[50]



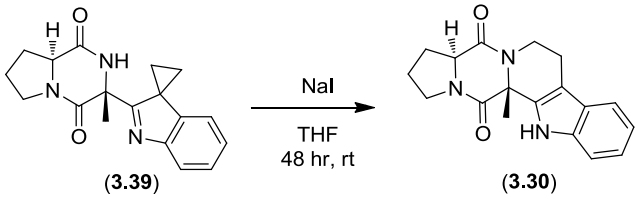
(**3.36**) (**3.38**)

To a solution of tosylate (**3.36**) (650 mg, 1.35 mmol) in THF (50 mL) was added 45% aqueous solution of KOH (576 µL, 6.75 mmol) and the solution was stirred at room temperature for 24 hours before diluting with water (30 mL) and extracting with EtOAc (3 x 80 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the crude. Purification of the crude by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate : petroleum ether, 3 : 1) afforded cyclised product (**3.38**) (208 mg, 29%) and cyclopropane (**3.39**) (122 mg, 50%) in a total yield of 79%.

M.P. 87-90 **ºC**; **$[\alpha]_D^{30}$** = - 154.6 (c = 0.95 in $CHCl_3$) (lit. $[\alpha]_D^{23}$ = - 132.5 (c = 0.33 in $CHCl_3$)); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.78 (s, 3H, C<u>H</u>$_3$C), 1.80-2.00 (m, 3H, NCHC<u>H</u>$_A$H$_B$, NCH$_2$C<u>H</u>$_2$CH$_2$), 2.39-2.46 (m,1H, NCHCH$_A$<u>H</u>$_B$), 2.73-2.78 (m, 2H, NCH$_2$C<u>H</u>$_2$C), 3.00-3.08 (m, 1H, NC<u>H</u>$_A$H$_B$CH$_2$C), 3.50-3.58 (m, 2H, NC<u>H</u>$_2$CH$_2$CH$_2$), 4.08 (dd, 1H, *J* = 9.8 Hz, *J* = 6.4 Hz, NC<u>H</u>CH$_2$), 4.93-4.99 (m, 1H, NCH$_A$<u>H</u>$_B$CH$_2$C) , 6.99-7.04 (m, 1H, Ar-H), 7.08-7.13 (m, 1H, Ar-H), 7.29 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.40 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.35 (br s, 1H, N-H); **^{13}C NMR: δ_C** (75 MHz, $CDCl_3$) 20.6 (NCH$_2$<u>C</u>H$_2$C), 21.8 (NCH$_2$<u>C</u>H$_2$CH$_2$), 26.2 (<u>C</u>H$_3$C), 29.9 (NCH$_2$CH$_2$<u>C</u>H$_2$), 37.1 (N<u>C</u>H$_2$CH$_2$C), 45.9 (N<u>C</u>H$_2$CH$_2$CH$_2$), 58.6 (N<u>C</u>HCH$_2$), 61.4 (CH$_3$<u>C</u>), 109.7 (Ar<u>C</u>-quat), 111.6 (Ar<u>C</u>-H), 118.4 (Ar<u>C</u>-H),

119.6 (ArC-H), 122.5 (ArC-H), 126.2 (ArC-quat), 132.8 (ArC-quat), 136.9 (ArC-quat), 165.9 (CO), 166.6 (CO); ***m/z* (ES$^+$)** 332 ([M+Na]$^+$, 100%).

7.3.1.5 Synthesis and characterisation of (3a*S*,12b*R*)-12b-methyl-1,2,3,3a,6,7,12,12b-octahydro-4*H*,13*H*-pyrrolo[1'',2'':4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indole-4,13-dione (**3.30**)[49]



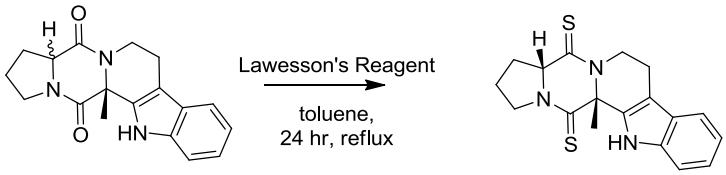
(**3.39**) (**3.30**)

To a solution of cyclopropane (**3.39**) (19 mg, 0.06 mmol) in THF (2 mL), was added NaI (18.5 mg, 0.12 mmol) and the solution was stirred at room temperature for 48 hours before evaporating the solvent *in vacuo* to afford the crude. Purification of the crude by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate : petroleum ether, 3 : 1) afforded cyclised product (**3.30**) (18.6 mg, 99%).

M.P. 169-172 **º**C (lit. 196-198 **º**C); **$[\alpha]_D^{30}$** = - 143.4 (c = 0.70 in $CHCl_3$) (lit. $[\alpha]_D^{23}$ = - 168.5 (c = 1.06 in $CHCl_3$)); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.73-1.88 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 1.90 (s, 3H, $CC\underline{H}_3$), 1.95-2.06 (m, 1H, $NCHC\underline{H}_AH_B$), 2.42-2.50 (m, 1H, $NCHCH_A\underline{H}_B$), 2.71 (dd, 1H, *J* = 15.7 Hz, *J* = 4.6 Hz, $NC\underline{H}CH_2$), 2.88 (ddd, 1H, *J* = 14.5 Hz, *J* = 10.9 Hz, *J* = 5.9 Hz, $NCH_2C\underline{H}_AH_BC$), 3.21 (ddd, 1H, *J* = 14.5 Hz, *J* = 12.0 Hz, *J* = 4.2 Hz, $NCH_2CH_A\underline{H}_BC$), 3.31 (ddd, 1H, *J* = 12.9 Hz, *J* = 10.9 Hz, *J* = 4.2 Hz, $NC\underline{H}_AH_BCH_2C$), 3.88-4.00 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 5.00 (ddd, 1H, *J* = 12.9 Hz, *J* = 5.9 Hz, *J* = 0.9 Hz, $NCH_A\underline{H}_BCH_2C$), 7.03 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.09-7.14 (m, 1H, Ar-H), 7.27 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.41 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.97 (br s, 1H, N-H); ***m/z* (ES$^+$)** 332 ([M+Na]$^+$, 100%).

7.3.2 Studies towards DKP cleavage

7.3.2.1 Synthesis and characterisation of (3a*R*,12b*R*)-12b-methyl-1,2,3,3a,6,7,12,12b-octahydro-4*H*,13*H*-pyrrolo[1'',2'':4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indole-4,13-dithione (**3.48**)



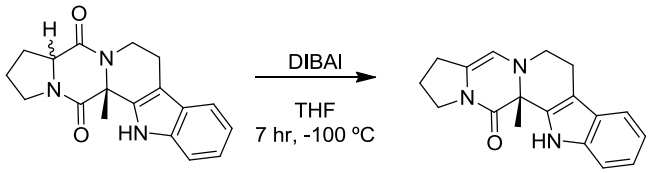
(**3.47**) (**3.48**)

To a solution of cyclised product (**3.47**) (608 mg, 1.97 mmol, 1.4 : 1 dr) in toluene (10 mL), was added Lawesson's Reagent (1.91 g, 4.72 mmol) and the solution was refluxed for 24 hours before cooling and evaporating the solvent *in vacuo* to afford the crude. Isolation of one diastereomer by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 0.5 : 9.5 to ethyl acetate : petroleum ether, 1 : 4) afforded cyclised product (**3.48**) as a colourless solid (241

mg, 36%). This was recrystalised (EtOAc/petroleum ether) and the absolute stereochemistry was proved by X-ray analysis.

M.P. 46-50 ºC; **$[\alpha]_D^{25}$** = - 61.0 (c = 0.34 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3327 (br w, N-H); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 2.02 (s, 3H, $C\underline{H}_3$), 2.04-2.09 (m, 1H, $NCH_2C\underline{H}_A\underline{H}_BCH_2$), 2.12-2.19 (m, 1H, $NCH_2CH_A\underline{H}_BCH_2$), 2.36-2.45 (m, 1H, $NCHC\underline{H}_A\underline{H}_B$), 2.91-3.00 (m, 3H, $NCHCH_A\underline{H}_B$, $NCH_2C\underline{H}_2C$), 3.38 (td, 1H, *J* = 12.5 Hz, *J* = 4.2 Hz, $NC\underline{H}_A\underline{H}_BCH_2C$), 3.85-3.92 (m, 1H, $NC\underline{H}_A\underline{H}_BCH_2CH_2$), 4.16 (dd, 1H, *J* = 14.3 Hz, *J* = 9.2 Hz, $NCH_A\underline{H}_BCH_2CH_2$), 4.43 (dd, 1H, *J* = 11.3 Hz, *J* = 5.8 Hz, $NC\underline{H}CH_2$), 6.26 (ddd, 1H, *J* = 12.5 Hz, *J* = 4.2 Hz, *J* = 1.8 Hz, $NCH_A\underline{H}_BCH_2C$), 7.14 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.25 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.45 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.52 (d, 1H, *J* = 7.9 Hz, Ar-H), 9.90 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 20.2 ($NCH_2\underline{C}H_2C$), 21.2 ($NCH_2\underline{C}H_2CH_2$), 27.3 ($\underline{C}H_3$), 35.4 ($NCH\underline{C}H_2$), 47.4 ($N\underline{C}H_2CH_2C$), 54.9 ($N\underline{C}H_2CH_2CH_2$), 66.8 ($N\underline{C}HCH_2$), 70.4 ($CH_3\underline{C}$), 111.9 (2C, Ar$\underline{C}$-quat, Ar$\underline{C}$-H), 118.7 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 122.9 (Ar$\underline{C}$-H), 126.1 (Ar$\underline{C}$-quat), 132.9 (Ar$\underline{C}$-quat), 137.2 (Ar$\underline{C}$-quat), 192.3 (CS), 194.4 (CS) ; ***m/z* (ES$^-$)** 340 ([M-H]$^-$, 90%); **HRMS ES (-)** Found 340.0955 for $C_{18}H_{18}N_3S_2$ [M-H]$^-$, requires 340.0948.

7.3.2.2 Synthesis and characterisation of (12b*R*)-12b-methyl-2,3,6,7,12,12b-hexahydro-1*H*,13*H*-pyrrolo[1'',2'':4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indol-13-one (**3.51**)



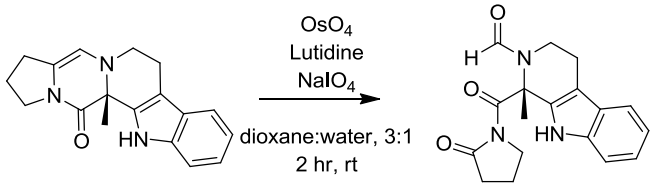
(**3.47**) (**3.51**)

To a solution of cyclised product (**3.47**) (204 mg, 0.66 mmol, 1.4 : 1 dr) in dry THF (7 mL), under N_2 at -100 ºC was added DIBAl (1 M in hexane) (0.76 mL, 0.76 mmol) dropwise over 10 minutes under N_2. The solution was stirred at -100 ºC for 7 hours before quenching with MeOH (1.2 mL), warming to room temperature and adding diethyl ether (15 mL) and 1 M aqueous HCl (5 mL). The solution was stirred at room temperature for 5 minutes before extracting with diethyl ether (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated *in vacuo* to afford the crude (180 mg, 93%) as a colourless solid which did not require further purification.

M.P. 67-72 ºC; **$[\alpha]_D^{25}$** = - 17.1 (c = 0.73 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3400 (br w, N-H), 1641 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.57 (s, 3H, $C\underline{H}_3C$), 1.83-1.94 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.45-2.66 (m, 3H, $NCH_2CH_2C\underline{H}_2$, $NCH_2C\underline{H}_A\underline{H}_BC$), 2.90 (ddd, 1H, *J* = 15.2 Hz, *J* = 11.5 Hz *J* = 5.9 Hz, $NCH_2CH_A\underline{H}_BC$), 3.18 (ddd, 1H, *J* = 12.7 Hz, *J* = 5.9 Hz, *J* = 1.4 Hz, $NC\underline{H}_A\underline{H}_BCH_2C$), 3.50 (ddd, 1H, *J* = 12.7 Hz, *J* = 11.5 Hz, *J* = 4.3 Hz, $NCH_A\underline{H}_BCH_2C$), 3.54-3.64 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 5.47 (t, 1H, *J* = 1.6 Hz, $NC\underline{H}C$), 6.98-7.03 (m, 1H, Ar-H), 7.06-7.11 (m, 1H, Ar-H), 7.28 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.41 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.96 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.7 ($\underline{C}H_3C$), 22.7 ($NCH_2\underline{C}H_2C$), 26.6 ($NCH_2\underline{C}H_2CH_2$), 31.6 ($NCH_2CH_2\underline{C}H_2$), 45.6 ($N\underline{C}H_2CH_2CH_2$), 46.3 ($N\underline{C}H_2CH_2C$), 59.7 ($CH_3\underline{C}$), 107.9 (C-quat), 111.4 (Ar$\underline{C}$-H), 113.2 ($NC\underline{C}H$), 116.4 (Ar$\underline{C}$-H), 118.1 (C-quat), 119.2 (Ar$\underline{C}$-H), 122.0 (Ar$\underline{C}$-H), 126.8 (C-quat), 134.6 (C-quat), 136.4 (C-quat), 164.4 (CO);

***m/z* (ES$^+$)** 316 ([M+Na]$^+$, 50%), 609 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 316.1420 for $C_{18}H_{19}N_3ONa^+$ [M+Na]$^+$, requires 316.1420.

7.3.2.3 Synthesis and characterisation of (1*R*)-1-methyl-1-[(2-oxopyrrolidin-1-yl)carbonyl]-1,3,4,9-tetrahydro-2*H*-β-carboline-2-carbaldehyde (**3.52**)

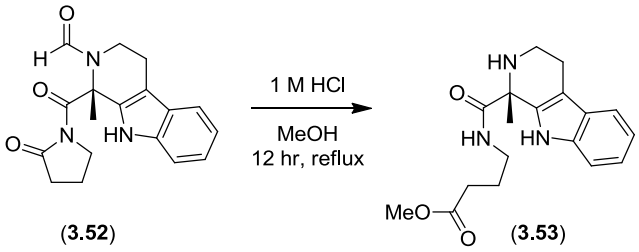


(**3.51**) (**3.52**)

A procedure developed by Jin and co-workers was followed.[54] To a solution of enamine (**3.51**) (50 mg, 0.17 mmol) in dioxane:water 3:1 (2 mL), was added lutidine (39 µL, 0.34 mmol), OsO_4 (2.5% in 2-methyl-2-propanol) (2 µL, 0.005 mmol) and $NaIO_4$ (55 mg, 0.26 mmol). The solution was stirred at room temperature for 2 hours before diluting with water (5 mL) and extracting with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford the crude. Purification of the crude by flash silica gel chromatography (ethyl acetate) afforded formamide (**3.52**) as a colourless solid (42 mg, 76%).

M.P. 206-208 ºC; **$[\alpha]_D^{25}$** = + 13.5 (c = 1.18 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3307 (br w, N-H), 1765 (s, C=O), 1668 (br s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.62-1.70 (m, 5H, C$\underline{H}_3$, NC(O)CH$_2$C$\underline{H}_2$CH$_2$), 2.22 (t, 2H, *J* = 8.0 Hz, NC(O)C$\underline{H}_2$CH$_2$CH$_2$), 2.79 (app. dd, 1H, *J* = 15.0 Hz, *J* = 3.6 Hz, CH$_3$CNCH$_2$C$\underline{H}_A$H$_B$), 3.03-3.13 (m, 1H, CH$_3$CNCH$_2$CH$_A$$\underline{H}_B$), 3.36-3.51 (m, 2H, CH$_3CNC\underline{H}_AH_BCH_2$, NC(O)CH$_2CH_2C\underline{H}_AH_B$), 3.72 (dt, 1H, *J* = 10.4 Hz, *J* = 7.4 Hz, NC(O)CH$_2$CH$_2$CH$_A$$\underline{H}_B$), 4.10 (app. dd, 1H, *J* = 13.1 Hz, *J* = 5.0 Hz, CH$_3$CNCH$_A$$\underline{H}_BCH_2$), 6.97 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.05 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.28 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.43 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.13 (br s, 1H, N-H), 10.90 (br s, 1H, CHO); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 18.5 (CH$_3$CNCH$_2$$\underline{C}H_2$), 21.0 (NC(O)CH$_2$$\underline{C}H_2CH_2$), 24.3 ($\underline{C}H_3$), 33.2 (NC(O)$\underline{C}H_2CH_2CH_2$), 42.7 (CH$_3CN\underline{C}H_2CH_2$), 47.6 (NC(O)CH$_2CH_2$$\underline{C}H_2$), 62.5 (CH$_3$$\underline{C}$), 109.4 (Ar$\underline{C}$-quat), 112.5 (Ar$\underline{C}$-H), 119.0 (Ar$\underline{C}$-H), 119.6 (Ar$\underline{C}$-H), 122.2 (Ar$\underline{C}$-H), 126.5 (Ar$\underline{C}$-quat), 131.2 (Ar$\underline{C}$-quat), 137.5 (Ar$\underline{C}$-quat), 162.9 (CO), 170.1 (CO), 174.2 (CO); ***m/z* (ES$^+$)** 348 ([M+Na]$^+$, 50%), 673 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 348.1324 for $C_{18}H_{19}N_3O_3Na^+$ [M+Na]$^+$, requires 348.1319.

7.3.2.4 Synthesis and characterisation of methyl 5-({[(1*R*)-1-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl]carbonyl}amino)-5-oxopentanoate (**3.53**)



(**3.52**) (**3.53**)

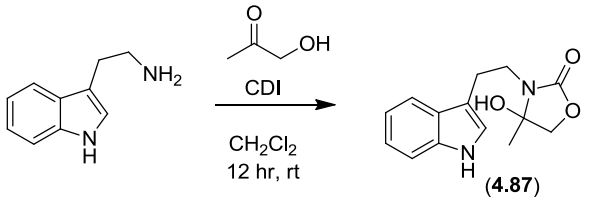
A solution of formamide (**3.52**) (13 mg, 0.04 mmol) in 1 M aqueous HCl (5 mL) and MeOH (3 mL) was refluxed for 12 hours before cooling and neutralising with a saturated solution of $NaHCO_3$. The solution was evaporated *in vacuo*, water added (10 mL) and extracted with EtOAc (3 x 10 mL) before drying over Na_2SO_4 and evaporating the solvent *in vacuo* to afford the crude (12 mg, 90%) as a colourless oil which did not require further purification.

$[\alpha]_D^{25}$ = + 7.0 (c = 1.86 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3325 (br m, N-H), 1734 (s, C=O), 1657 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.65 (s, 3H, CH_3C), 1.85 (p, 2H, *J* = 7.2 Hz, $NCH_2CH_2CH_2$), 2.34 (t, 2H, *J* = 7.2 Hz, $NCH_2CH_2CH_2$), 2.65-2.72 (m, 1H, $NCH_2CH_AH_BC$), 2.73-2.79 (m, 1H, $NCH_2CH_AH_BC$), 2.87-2.94 (ddd, 1H, *J* = 13.2 Hz, *J* = 9.3 Hz, *J* = 4.1 Hz, $NCH_AH_BCH_2C$), 3.22-3.34 (m, 3H, $NCH_2CH_2CH_2$, $NCH_AH_BCH_2C$), 3.65 (s, 3H, OCH_3), 7.08 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.15 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.35 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.48 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.98 (br s, 1H, N-H), 8.83 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 22.9 (NCH_2CH_2C), 24.8 ($NCH_2CH_2CH_2$), 28.3 (CH_3C), 31.4 ($NCH_2CH_2CH_2$), 38.5 ($NCH_2CH_2CH_2$), 41.5 (NCH_2CH_2C), 51.7 (OCH_3), 58.0 (CH_3C), 108.9 (ArC-quat), 111.3 (ArC-H), 118.2 (ArC-H), 119.2 (ArC-H), 121.8 (ArC-H), 126.7 (ArC-quat), 134.8 (ArC-quat), 136.2 (ArC-quat), 173.5 (CO), 174.7 (CO); ***m/z* (ES$^+$)** 330 ($[M+H]^+$, 75%), 352 ($[M+Na]^+$, 65%); **HRMS ES (+)** Found 352.1630 for $C_{18}H_{23}N_3O_3Na^+$ $[M+Na]^+$, requires 352.1632.

7.4 Experimental for chapter 4

7.4.1 Synthesis of oxazolidinone (**4.85**) and oxazolidinethione (**4.90**)

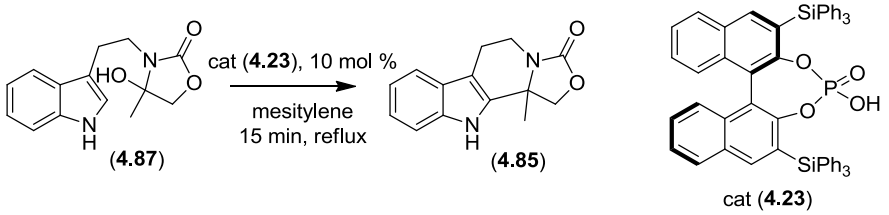
7.4.1.1 Synthesis and characterisation of (±)-4-hydroxy-3-[2-(1*H*-indol-3-yl)ethyl]-4-methyl-1,3-oxazolidin-2-one (**4.87**)



To a stirring solution of CDI (5.06 g, 31.2 mmol) in anhydrous CH_2Cl_2 (75 mL) was added a solution of hydroxy acetone (2.13 mL, 31.2 mmol) in anhydrous CH_2Cl_2 (75 mL) at 0 ºC and the solution was stirred at room temperature for 1.5 hours before the portion wise addition of tryptamine (5 g, 31.2 mmol). The solution was stirred at room temperature for 12 hours before the addition of a saturated solution of $NaHCO_3$ (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic layers were washed with brine (50 mL) before filtering through a phase separator funnel and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to 3 : 1) afforded the titled compound as a colourless solid (4.12 g, 51%)

M.P. 132-134 **º**C; **ν_{max}(film)/cm^{-1}** 3324 (br w, N-H, O-H), 1731 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.37 (s, 3H, C$\underline{H}_3$C), 2.89-3.04 (m, 2H, NCH$_2$C$\underline{H}_2$), 3.30-3.39 (m, 2H, NC$\underline{H}_2$CH$_2$), 4.07 (d, 1H, *J* = 9.3 Hz, CO$_2$C$\underline{H}_A$H$_B$), 4.11 (d, 1H, *J* = 9.3 Hz, CO$_2$CH$_A\underline{H}_B$), 6.35 (br s, 1H, O-H), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.08 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.21 (d, 1H, *J* = 1.7 Hz, NHC$\underline{H}$), 7.35 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.57 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.85 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 25.3 (C$\underline{H}_3$C), 26.0 (NCH$_2$C$\underline{H}_2$), 41.0 (NC$\underline{H}_2$CH$_2$), 75.7 (CO$_2$C$\underline{H}_2$), 86.7 (CH$_3$C), 112.2 (ArC-quat), 112.3 (ArC-H), 119.0 (ArC-H), 119.2 (ArC-H), 121.8 (ArC-H), 123.7 (NHCH), 128.0 (ArC-quat), 137.1 (ArC-quat), 157.5 (CO); ***m/z* (ES$^+$)** 283 ([M+Na]$^+$, 35%), 543 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 283.1052 for $C_{14}H_{16}N_2O_3Na^+$ [M+Na]$^+$, requires 283.1053.

7.4.1.2 Synthesis and characterisation of 11b-methyl-5,6,11,11b-tetrahydro-1*H*-[1,3]oxazolo[3',4':1,2]pyrido[3,4-*b*]indol-3-one (**4.85**)

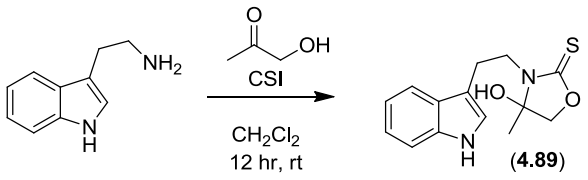


To a solution of aminol (**4.87**) (78 mg, 0.3 mmol) in refluxing mesitylene (63 mL) was added catalyst (**4.23**) (26 mg, 0.03 mmol) and the solution was refluxed for 15 minutes before cooling and

evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (ethyl acetate : petroleum ether, 2 : 3) afforded the titled compound as a colourless solid (60 mg, 83%). The ee was determined by HPLC using a Chiralpak OD-H column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 8.0 min, minor t_R = 11.6 min (44% ee).

M.P. 145-150 ºC; **$[\alpha]_D^{25}$** = + 55.4 (c = 1.28 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3294 (br w, N-H), 1729 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.74 (s, 1H, C$\underline{H}_3$), 2.80 (app. dd, 1H, *J* = 15.7 Hz, *J* = 4.7 Hz, NCH$_2$C$\underline{H}_A$H$_B$), 3.04 (ddd, 1H, *J* = 15.7 Hz, *J* = 12.0 Hz, *J* = 6.2 Hz, NCH$_2$CH$_A$$\underline{H}_B$), 3.35 (ddd, 1H, *J* = 13.7 Hz, *J* = 12.0 Hz, *J* = 4.7 Hz, NC$\underline{H}_A$H$_B$CH$_2$), 4.21 (app. dd, 1H, *J* = 13.7 Hz, *J* = 6.2 Hz, NCH$_A$$\underline{H}_BCH_2$), 4.37-4.41 (m, 1H, OC$\underline{H}_AH_B$C), 4.49-4.53 (m, 1H, OCH$_A$$\underline{H}_B$C), 7.15 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.21 (t, 1H, *J* = 7.0 Hz, Ar-H), 7.37 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.22 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.4 (C$\underline{H}_2$), 25.5 (C$\underline{H}_3$), 37.4 (C$\underline{H}_2$), 58.3 (CH$_3$C), 74.1 (OC$\underline{H}_2$C), 107.6 (ArC-quat), 111.5 (ArC-H), 118.5 (ArC-H), 119.8 (ArC-H), 122.5 (ArC-H), 126.4 (ArC-quat), 134.4 (ArC-quat), 136.4 (ArC-quat), 158.5 (CO); ***m/z* (ES$^+$)** 265 ([M+Na]$^+$, 25%), 507 ([2M+Na]$^+$, 85%); **HRMS ES (+)** Found 265.0947 for $C_{14}H_{14}NO_2Na^+$ [M+Na]$^+$, requires 265.0947.

7.4.1.3 Synthesis and characterisation of (±)-4-hydroxy-3-[2-(1*H*-indol-3-yl)ethyl]-4-methyl-1,3-oxazolidine-2-thione (**4.89**)



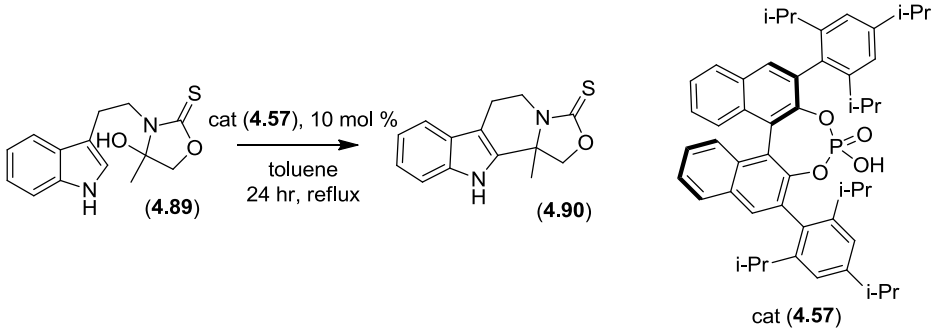
(**4.89**)

To a stirring solution of CSI (5.56 g, 31.2 mmol) in anhydrous CH_2Cl_2 (75 mL) was added a solution of hydroxy acetone (2.13 mL, 31.2 mmol) in anhydrous CH_2Cl_2 (75 mL) at 0 ºC and the solution was stirred at room temperature for 2 hours before the portion wise addition of tryptamine (5 g, 31.2 mmol). The solution was stirred at room temperature for 12 hours before the addition of a saturated solution of $NaHCO_3$ (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic layers were washed with brine (50 mL) before filtering through a phase separator funnel and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (ethyl acetate : hexane, 1 : 1) afforded the titled compound as a colourless solid (6 g, 70%).

M.P. 114-117 ºC; **ν_{max}(film)/cm^{-1}** 3409 (br m, N-H, O-H), 1168 (m, C=S); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.49 (s, 3H, C$\underline{H}_3$), 3.02-3.26 (m, 2H, NCH$_2$C$\underline{H}_2$), 3.62-3.74 (m, 2H, NC$\underline{H}_2$CH$_2$), 4.31 (d, 1H, *J* = 9.9 Hz, CH$_3$CC$\underline{H}_A$H$_B$), 4.37 (d, 1H, *J* = 9.9 Hz, CH$_3$CCH$_A$$\underline{H}_B$), 6.89 (s, 1H, O-H), 7.02 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.09 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.23 (d, 1H, *J* = 2.0 Hz, NHC$\underline{H}$), 7.36 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.73 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.88 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 24.7 (NCH$_2$C$\underline{H}_2$), 25.0 (C$\underline{H}_3$), 44.4 (NC$\underline{H}_2$CH$_2$), 79.1 (OC$\underline{H}_2$C), 90.8 (CH$_3$C), 111.9 (ArC-H), 112.3 (ArC-H), 119.3 (2 x ArC-H) , 121.9 (ArC-quat), 123.9 (NHC$\underline{H}$), 128.0 (ArC-quat), 137.1 (ArC-

quat), 187.2 (CS); ***m/z* (ES$^+$)** 299 ([M+Na]$^+$, 55%), 575 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 299.0821 for $C_{14}H_{16}N_2O_2SNa^+$ [M+Na]$^+$, requires 299.0825.

7.4.1.4 Synthesis and characterisation of 11b-methyl-5,6,11,11b-tetrahydro-1*H*-[1,3]oxazolo[3',4':1,2]pyrido[3,4-*b*]indole-3-thione (**4.90**)

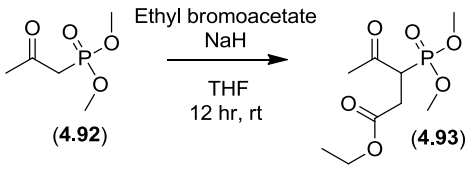


To a solution of aminol (**4.89**) (83 mg, 0.3 mmol) in refluxing toluene (42 mL) was added catalyst (**4.57**) (23 mg, 0.03 mmol) and the solution was refluxed for 24 hours before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (CH_2Cl_2) afforded the titled compound as a colourless solid (76 mg, 98%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 6.6 min, major t_R = 8.3 min (18% ee).

M.P. 65-69 **ºC**; **$[\alpha]_D^{25}$** = + 36.0 (c = 0.95 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3264 (br w, N-H), 1227 (s, C=S); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.73 (s, 3H, C$\underline{H}_3$), 2.87 (app. dd, 1H, *J* = 15.6 Hz, *J* = 4.8 Hz, NCH$_2$C$\underline{H}_A$H$_B$), 3.01-3.11 (m, 1H, NCH$_2$CH$_A\underline{H}_B$), 3.51 (app. td, 1H, *J* = 13.0 Hz, *J* = 4.8 Hz, N$\underline{H}_A$H$_B$CH$_2$), 4.48 (dd, 1H, *J* = 8.6 Hz, *J* = 2.4 Hz, OC$\underline{H}_A$H$_B$C), 4.62 (dd, 1H, *J* = 8.6 Hz, *J* = 2.4 Hz, OCH$_A\underline{H}_B$C), 4.75 (dd, 1H, *J* = 13.0 Hz, *J* = 6.1 Hz, NCH$_A\underline{H}_B$CH$_2$), 7.11-7.21 (m, 2H, 2 x Ar-H), 7.35 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.90 (br d, 1H, *J* = 5.8 Hz, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.4 (NCH$_2\underline{C}$H$_2$), 25.2 (C$\underline{H}_3$), 40.9 (N$\underline{C}$H$_2$CH$_2$), 62.2 (CH$_3\underline{C}$), 78.0 (O$\underline{C}$H$_2$C), 107.6 (Ar$\underline{C}$-quat), 111.5 (Ar$\underline{C}$-H), 118.7 (Ar$\underline{C}$-H), 120.1 (Ar$\underline{C}$-H), 122.8 (Ar$\underline{C}$-H), 126.1 (Ar$\underline{C}$-quat), 133.0 (Ar$\underline{C}$-quat), 136.5 (Ar$\underline{C}$-quat), 186.2 (CS); ***m/z* (ES$^-$)** 257 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 281.0719 for $C_{14}H_{14}N_2OSNa^+$ [M+Na]$^+$, requires 281.0719.

7.4.2 Synthetic strategy to 3-methylene amide (**4.96**)

7.4.2.1 Synthesis and characterisation of ethyl 3-(dimethoxyphosphoryl)-4-oxopentanoate (**4.93**)

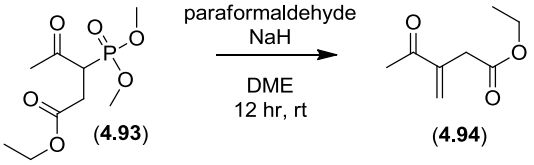


A solution of dimethyl (2-oxopropyl)phosphonate (4.85 mL, 25 mmol) in THF (5 mL) under N_2, was added to a stirring solution of NaH (1 g, 25 mmol) in THF (50 mL) at 0 ºC. The solution was

warmed to room temperature and stirred for 1 hour before the addition of ethyl bromoacetate (3.32 mL, 25 mmol). The solution was stirred at room temperature for 12 hours before the pouring into a 5% aqueous HCl solution (100 mL) and extracting with CH_3Cl (3 x 50 mL). The combined organic layers were filtered through a phase separator funnel and the solvent evaporated *in vacuo* to afford the crude. The crude was purified by vacuum distillation (120 ºC, 1 mbar) to afford the titled product (4.15 g, 66%) as a colourless oil.

ν_{max}(film)/cm^{-1} 1720 (br s, C=O), 1247 (br s, P=O), 1032 (br s, P-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.21 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 2.39 (s, 3H, C(O)C$\underline{H}_3$), 2.62-2.71 (ddd, 1H, *J* = 17.8 Hz, *J* = 9.4 Hz, *J* = 3.2 Hz, C$\underline{H}_A$H$_B$CO$_2$Et), 3.05-3.16 (m, 1H, CH$_A\underline{H}_B$CO$_2$Et), 3.63-3.72 (m, 1H, C(O)C$\underline{H}$), 3.73 (s, 3H, P(O)OC$\underline{H}_3$), 3.76 (s, 3H, P(O)OC$\underline{H}_3$), 4.09 (q, 1H, *J* = 7.2 Hz, C$\underline{H}_2$CH$_3$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 31.2 (d, *J* = 2.7 Hz, C(O)$\underline{C}$H$_2$CH), 31.4 (C(O)$\underline{C}$H$_3$), 47.3 (P(O)O$\underline{C}$H$_3$), 48.5 (P(O)O$\underline{C}$H$_3$), 53.5 (dd, *J* = 28.0 Hz, *J* = 6.7Hz, C(O)$\underline{C}$H), 61.2 ($\underline{C}H_2CH_3$), 171.3 (d, *J* = 19.4 Hz, CO), 202.2 (d, *J* = 4.4 Hz, CO); ***m/z* (ES$^+$)** 253 ([M+H]$^+$, 75%), 275 ([M+Na]$^+$, 80%); **HRMS ES (+)** Found 275.0657 for $C_9H_{17}O_6PNa^+$ [M+Na]$^+$, requires 275.0655.

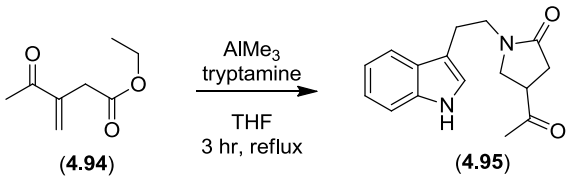
7.4.2.2 Synthesis and characterisation of ethyl 3-methylene-4-oxopentanoate (**4.94**)



To a solution of NaH (307 mg, 7.7 mmol) in anhydrous DME (14 mL) under N_2, was added a solution of phosphonate (**4.93**) (1.6 g, 7.7 mmol) in anhydrous DME (6 mL) under N_2 at -20 ºC. The solution was warmed to room temperature and stirred for 1 hour before the addition of paraformaldehyde (232 mg, 7.7 mmol). The solution was stirred at room temperature for 12 hours and water (100 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were filtered through a phase separator funnel and the solvent evaporated *in vacuo* to afford the crude (1.2 g, 99%) as a colourless oil which did not require further purification.

ν_{max}(film)/cm^{-1} 1736 (s, C=O), 1681 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.25 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.38 (s, 3H, C(O)C$\underline{H}_3$), 3.29 (s, 2H, CC$\underline{H}_2$C(O)), 4.14 (q, 2H, *J* = 7.1 Hz, C$\underline{H}_2$CH$_3$), 5.95-5.97 (m, 1H, C$\underline{H}_A$H$_B$=C), 6.17 (d, 1H, *J* = 3.5 Hz, CH$_A\underline{H}_B$=C); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 25.4 (C(O)$\underline{C}$H$_3$), 36.8 (C$\underline{C}$H$_2$C(O)), 60.8 ($\underline{C}H_2CH_3$), 128.0 ($\underline{C}$H$_2$=C), 142.5 (CH$_2$=$\underline{C}$), 171.0 (CO), 198.5 (CO); ***m/z* (ES$^+$)** 179 ([M+Na]$^+$, 25%), 335 ([2M+Na]$^+$, 65%); **HRMS ES (+)** Found 179.0679 for $C_8H_{12}O_3Na^+$ [M+Na]$^+$, requires 179.0679.

7.4.2.3 Synthesis and characterisation of 4-acetyl-1-[2-(1*H*-indol-3-yl)ethyl]pyrrolidin-2-one (**4.95**)



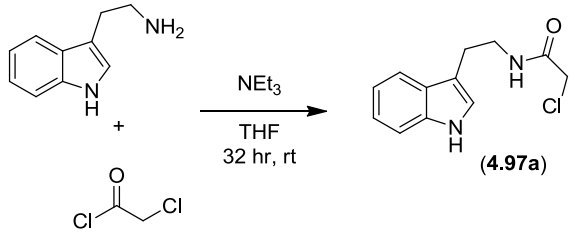
(**4.94**) (**4.95**)

To a solution of tryptamine (120 mg, 0.75 mmol) in THF (3 mL) at 0 ºC under N_2 was added $AlMe_3$ and alkene (**4.94**) (51 mg, 0.38 mmol) and the solution was refluxed for 3 hours before cooling and adding a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were filtered through a phase separator funnel and the solvent evaporated *in vacuo* to afford the crude. The crude was purified by flash silica gel chromatography (ethyl acetate : hexane, 1 : 1) to afford the titled compound as a colourless solid (77 mg, 77%).

M.P. 101-103 **º**C; **ν_{max}(film)/cm^{-1}** 3283 (br w, N-H), 1722 (s, C=O), 1666 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.12 (s, 3H, C(O)C$\underline{H}_3$), 2.61 (d, 2H, *J* = 8.0 Hz, C(O)C$\underline{H}_2$CH), 3.02 (t, 2H, *J* = 7.2 Hz, NCH$_2$C$\underline{H}_2$), 3.13-3.23 (m, 1H, C(O)C$\underline{H}$), 3.35-3.42 (m, 1H, NC$\underline{H}_A$H$_B$CH), 3.52 (dd, 1H, *J* = 9.7 Hz, *J* = 6.3 Hz, NCH$_A$$\underline{H}_B$CH), 3.57-3.70 (m, 2H, NC$\underline{H}_2$CH$_2$), 7.04 (d, 1H, *J* = 1.0 Hz, NHC$\underline{H}$), 7.13 (t, 1H, *J* = 7.7 Hz, Ar-H), 7.20 (t, 1H, *J* = 7.7 Hz, Ar-H), 7.37 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.61 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.27 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 23.2 (C(O)$\underline{C}$H$_2$CH), 28.3 (C(O)$\underline{C}$H$_3$), 33.3 (NCH$_2$$\underline{C}H_2$), 43.1 (N$\underline{C}H_2CH_2$), 43.5 (C(O)$\underline{C}$H), 48.1 (N$\underline{C}H_2$CH), 111.3 (Ar$\underline{C}$-H), 112.6 (Ar$\underline{C}$-quat), 118.5 (Ar$\underline{C}$-H), 119.4 (Ar$\underline{C}$-H), 122.0 & 122.1 (Ar$\underline{C}$-H, NH$\underline{C}$H), 127.3 (Ar$\underline{C}$-quat), 136.3 (Ar$\underline{C}$-quat), 172.1 (CO), 206.0 (CO); ***m/z* (ES$^+$)** 293 ([M+Na]$^+$, 30%), 563 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 293.1254 for $C_{16}H_{18}N_2O_2Na^+$ [M+Na]$^+$, requires 293.1260.

7.4.3 Synthesis of iodo compounds (**4.99a**) and (**4.99b**)

7.4.3.1 Synthesis and characterisation of 2-chloro-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (**4.97a**)[82]



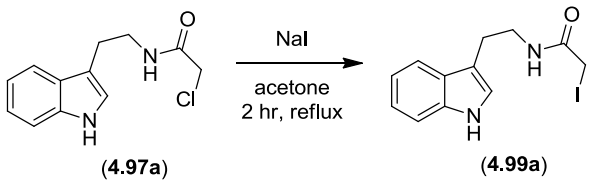
(**4.97a**)

To a solution of tryptamine (10 g, 62.4 mmol) in dry THF (100 mL) was added a solution of chloroacetyl chloride (5.9 mL, 74.9 mmol) in dry THF (100 mL) followed by the addition of a solution of NEt_3 (20.7 mL, 150 mmol) in dry THF (150 mL) at room temperature. The solution was stirred at room temperature for 32 hours before filtering through a sintered funnel. The solvent was evaporated *in vacuo* and the residue was redissolved in CH_2Cl_2 (100 mL), then successively

washed with 0.5 M aqueous HCl (100 mL), saturated aqueous Na_2CO_3 (100 mL) and water (100 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the crude (13.8 g, 94%), which did not require further purification.

M.P. 69-74 **ºC**; **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 3.05 (t, 2H, *J* = 6.8 Hz, $NHCH_2C\underline{H}_2$), 3.67 (app. dd, 2H, *J* = 12.8 Hz, *J* = 2.6 Hz, $NHC\underline{H}_2CH_2$), 4.04 (s, 2H, $C(O)C\underline{H}_2Cl$) , 6.68 (br s, 1H, N-H), 7.08 (d, 1H, *J* = 2.0 Hz, $NHC\underline{H}$), 7.17(t, 1H, *J* = 7.6 Hz, Ar-H), 7.25 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.41 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.64 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.13 (br s, 1H, N-H); ***m/z* (ES$^+$)** 237 ($[M+H]^+$, 90%).

7.4.3.2 Synthesis and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-2-iodoacetamide (**4.99a**)

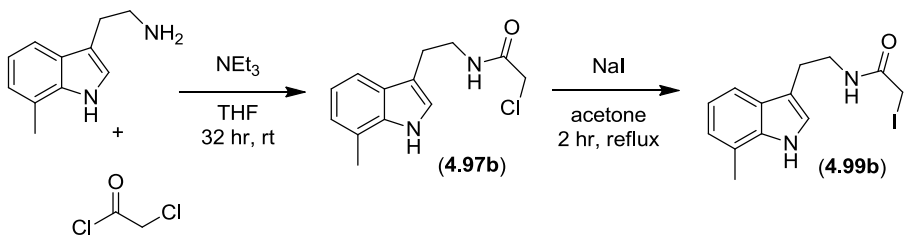


(**4.97a**) (**4.99a**)

Chloride (**4.97a**) (13.8 g, 58.3 mmol) was dissolved in acetone (250 mL) and NaI (9.35 g, 62.4 mmol) was added in one portion. The suspension was refluxed for 2 hours before cooling to room temperature and filtering. The solution was concentrated *in vacuo* to afford the crude title product which was further purified by flash silica gel chromatography (petroleum ether : ethyl acetate, 1 : 1), to yield a pale yellow solid (16.8 g, 82%).

M.P. 78-82 ^{o}C; **ν_{max}(film)/cm^{-1}** 3292 (br w, O-H, N-H), 1647 (C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 2.81 (t, 2H, *J* = 7.5 Hz, $NCH_2C\underline{H}_2C$), 3.29-3.40 (m, 2H, $NC\underline{H}_2CH_2C$), 3.64 (s, 2H, $IC\underline{H}_2C(O)N$), 6.95-7.01 (m, 1H, Ar-H), 7.02-7.09 (m, 1H, Ar-H), 7.15 (d, 1H, *J* = 2.0 Hz, $NHC\underline{H}$), 7.33 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.53 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.37 (t, 1H, *J* = 5.5 Hz, $N\underline{H}CH_2$), 10.84 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 2.0 ($I\underline{C}H_2C(O)N$), 25.6 ($NCH_2\underline{C}H_2C$), 40.8 ($N\underline{C}H_2CH_2C$), 112.2 (Ar*C*-quat), 112.3 (Ar*C*-H), 119.1 (2 x Ar*C*-H), 121.8 (Ar*C*-H), 123.6 ($NH\underline{C}H$), 128.0 (Ar*C*-quat), 137.1 (Ar*C*-quat), 168.3 (CO); ***m/z* (ES$^+$)** 387 ($[M+MeCN+NH_4]^+$, 100%); **HRMS ES (+)** Found 350.9965 for $C_{12}H_{13}N_2OINa^+$ $[M+Na]^+$ requires 350.9965.

7.4.3.2 Synthesis and characterisation of 2-iodo-*N*-[2-(7-methyl-1*H*-indol-3-yl)ethyl]acetamide (**4.99b**)



(**4.97b**) (**4.99b**)

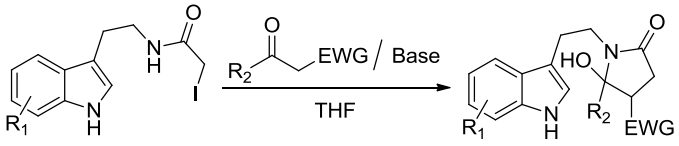
To a solution of 7-methyl tryptamine (939 mg, 5.39 mmol) in dry THF (20 mL) was added a solution of chloroacetyl chloride (515 µL, 6.47 mmol) in dry THF (20 mL) followed by the addition of a solution of NEt_3 (1.80 mL, 12.94 mmol) in dry THF (30 mL) at room temperature. The solution was

stirred at room temperature for 32 hours before filtering through a sintered funnel. The solvent was evaporated *in vacuo* and the residue was redissolved in CH_2Cl_2 (20 mL), then successively washed with 0.5 M aqueous HCl (20 mL), saturated aqueous Na_2CO_3 (20 mL) and water (20 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford crude 2-chloro-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (1.35 g), which did not require further purification.

The crude was dissolved in acetone (20 mL) and NaI (807 mg, 5.39 mmol) was added in one portion. The suspension was refluxed for 2 hours before cooling to room temperature and filtering. The solution was concentrated *in vacuo* to afford the crude title product which was further purified by flash silica gel chromatography (petroleum ether : ethyl acetate, 1 : 1), to yield a pale yellow solid (1.51 g, 82%).

M.P. 110-112 ^{o}C; **ν_{max}(film)/cm^{-1}** 3407 (m br, N-H), 3291 (m br, N-H), 1651 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.51 (s, 3H, C$\underline{H}_3$C), 3.00 (t, 2H, *J* = 6.5 Hz, NCH$_2$C$\underline{H}_2$C), 3.58-3.65 (m, 4H, NC$\underline{H}_2$CH$_2$C, IC$\underline{H}_2$C(O)N), 6.14 (br s, 1H, N-H), 7.02-7.12 (m, 3H, NHC$\underline{H}$, 2 x Ar-H), 7.48 (d, 1H, *J* = 7.5 Hz, Ar-H), 8.09 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) -0.2 (I$\underline{C}$H$_2$C(O)N), 16.7 ($\underline{C}$H$_3$C), 25.1 (NCH$_2\underline{C}$H$_2$C), 40.6 (N$\underline{C}$H$_2$CH$_2$C), 113.0 (Ar$\underline{C}$-quat), 116.4 (Ar$\underline{C}$-H), 119.8 (Ar$\underline{C}$-H), 120.6 (Ar$\underline{C}$-quat), 122.1 (NH$\underline{C}$H), 122.8 (Ar$\underline{C}$-H), 126.7 (Ar$\underline{C}$-quat), 136.1 (Ar$\underline{C}$-quat), 166.8 (CO); ***m/z* (ES$^+$)** 401 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS (ES+)** Found 365.0116 for $C_{13}H_{15}IN_2ONa^+$ [M+Na]$^+$, requires 365.0121.

7.4.4 Synthesis of hydroxylactams (**4.100**)-(**4.112**)



Entry	Compound no.	R_1	R_2	EWG	Yield
1	(**4.100**)	H	Me	P(O)(OMe)$_2$	60%
2	(**4.106**)	H	Me	P(O)(OEt)$_2$	40%
3	(**4.107**)	H	Me	CO_2Me	56%
4	(**4.108**)	H	Me	CO_2Et	38%
5	(**4.109**)	H	Et	CO_2Me	43%
6	(**4.110**)	H	n-pentyl	P(O)(OMe)$_2$	34%
7	(**4.111**)	H	Me	SO_2Me	62%
8	(**4.112**)	7-Me	Me	SO_2Ph	89%

General procedure for the preparation of hydroxylactams (**4.100**)-(**4.112**)

Method A:

To a stirred solution of nucleophile (2 equivalents) in THF (10 mL per mmol of nucleophile) under N_2, at 0 °C, was added a solution of KHMDS 0.5 M in toluene (1.2 equivalents), and the solution was warmed to room temperature and stirred for 1 hour. The solution was cooled to 0 °C and a

solution of tryptamine derivative (1 equivalent) in THF (2.5 mL per mmol of electrophile) was added. The solution was allowed to warm up to room temperature and stirred until the reaction had reached completion before quenching with water (10 mL per mmol of electrophile) and extracting with CH_2Cl_2 (3 x 15 mL per mmol of electrophile). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The solid residue was either triturated with ethyl acetate or purified by column chromatography on silica gel (petroleum ether/ethyl acetate) before triturating with ethyl acetate to afford the hydroxylactam.

Method B:

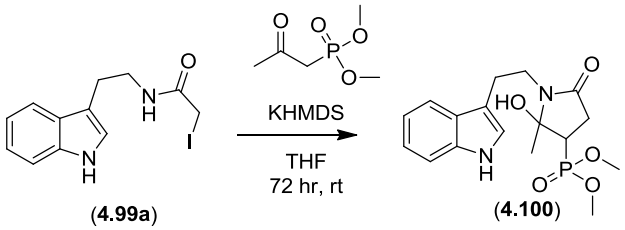
To a solution of NaH (1 equivalent) in THF (13 mL per mmol) under N_2 at 0 °C was added a solution of nucleophile (1 equivalent) in THF (2 mL per mmol), and the solution was stirred at room temperature for 1 hour. Solid tryptamine derivative (1 equivalent) was added to the solution, and the mixture was stirred at room temperature until the reaction had reached completion. The reaction was quenched by addition of water (30 mL per mmol) and extracted with CH_2Cl_2 (3 x 30 mL per mmol). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude residue was further purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate.

Method C:

Same procedure as method A using a solution of LHMDS (1M in toluene) instead of KHMDS.

A column chromatography on silica gel was performed as purification method, eluting with petroleum ether/ethyl acetate.

7.4.4.1 Synthesis and characterisation of (±)-dimethyl {2-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxopyrrolidin-3-yl}phosphonate (**4.100**)



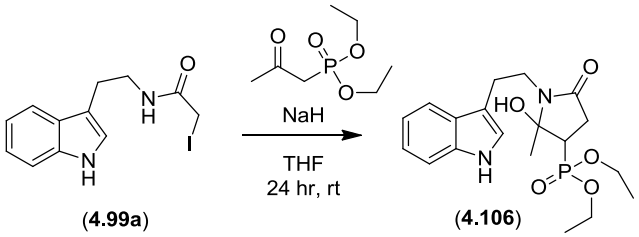
(**4.99a**) (**4.100**)

Following general procedure A (1.0 mmol scale of tryptamine derivative) the titled compound was obtained after 72 hours at room temperature as a colourless solid following trituration with ethyl acetate (208 mg, 60%).

M.P. 141-144 °C; **ν_{max}(film)/cm^{-1}** 3268 (br w, N-H, O-H), 1681 (s, C=O), 1266 (s, P=O), 1100 (s, P-O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 0.74 (s, 3H, C$\underline{H}_3$C), 1.48-1.59 (m, 1H, C(O)C$\underline{H}_A$H$_B$CH), 1.66-1.79 (m, 1H, C(O)CH$_A\underline{H}_B$CH), 1.87-2.02 (m, 2H, NCH$_2$C$\underline{H}_A$H$_B$C, C(O)CH$_2$C$\underline{H}$), 2.03-2.14 (m, 1H, NCH$_2$CH$_A\underline{H}_B$C), 2.38-2.48 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$C), 2.50-2.58 (m, 1H, NCH$_A\underline{H}_B$CH$_2$C), 3.63 (d, 3H, *J* = 5.6 Hz, OC$\underline{H}_3$), 3.66 (d, 3H, *J* = 5.6 Hz, OC$\underline{H}_3$), 6.22 (s, 1H, O-H), 7.00 (t, 1H, *J* = 7.7 Hz, Ar-H), 7.05-7.10 (m, 1H, Ar-H), 7.19 (d, 1H, *J* = 2.2 Hz, NHC$\underline{H}$), 7.34 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.58

(d, 1H, J = 7.7 Hz, Ar-H), 10.84 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 25.0 (C(O)$\underline{C}H_2$CH), 26.1 ($\underline{C}H_3$C), 30.6 (d, *J* = 4 Hz, NCH$_2\underline{C}H_2$C), 40.1 (N$\underline{C}H_2CH_2$C), 41.2 (d, *J* = 152 Hz, C(O)CH$_2\underline{C}$H), 51.7 (d, *J* = 6 Hz, O$\underline{C}H_3$), 52.7 (d, *J* = 6 Hz, O$\underline{C}H_3$), 88.9 (CH$_3\underline{C}$), 111.5 (NH$\underline{C}$H), 111.7 (Ar$\underline{C}$-quat), 118.3 (Ar$\underline{C}$-H), 118.3 (Ar$\underline{C}$-H), 121.0 (Ar$\underline{C}$-H), 122.8 (Ar$\underline{C}$-H), 127.1 (Ar$\underline{C}$-quat),136.2 (Ar$\underline{C}$-quat), 166.8 (CO); ***m/z* (ES$^+$)** 425 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 389.1221 for $C_{17}H_{23}N_2O_5PNa^+$ [M+Na]$^+$, requires 389.1237.

7.4.4.2 Synthesis and characterisation of (±)-diethyl {2-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxopyrrolidin-3-yl}phosphonate (**4.106**)

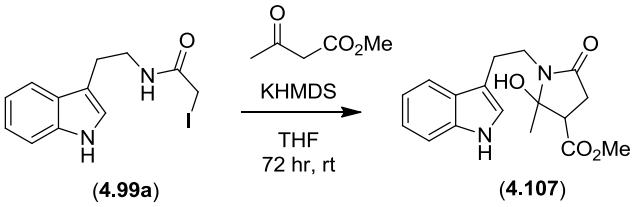


(**4.99a**) (**4.106**)

Following general procedure B (3.0 mmol scale of tryptamine derivative) the titled compound was obtained as a mixture of diastereomers (9.5 : 1) after 24 hours at room temperature as a colourless solid following trituration with ethyl acetate (481 mg, 40%).

M.P. 138-142 ºC; **ν_{max}(film)/cm^{-1}** 3283 (br w, N-H, O-H), 1679 (s, C=O), 1225 (s, P=O), 1056 (s, P-O), 1023 (s, P-O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.16-1.27 (m, 6H, 2 x CH$_2\underline{C}H_3$, minor diastereomer underneath), 1.59 (s, 3H, $\underline{C}H_3$C), 2.33-2.42 (m, 1H, C(O)C$\underline{H}_A$H$_B$CH), 2.52-2.77 (m, 2H, C(O)CH$_A\underline{H}_B$CH, C(O)CH$_2\underline{C}$H), 2.78-2.99 (m, 2H, C$\underline{H}_2$), 3.23-3.43 (m, 2H, C$\underline{H}_2$, minor diastereomer at 3.67 ppm), 3.95-4.11 (m, 4H, 2 x C$\underline{H}_2$CH$_3$, minor diastereomers at 3.76-3.87 ppm), 6.12 (s, 1H, O-H), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.07 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.15-7.20 (m, 1H, NHC$\underline{H}$, minor diastereomer underneath), 7.34 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58 (d, 1H, *J* = 7.8 Hz, Ar-H, minor diastereomer at 7.49 ppm), 10.84 (br s, 1H, N-H, minor diastereomer at 10.89 ppm); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 17.2 (app. t, *J* = 5.3 Hz, 2 x CH$_2\underline{C}H_3$), 25.9 (NCH$_2\underline{C}H_2$), 27.1 ($\underline{C}H_3$C), 31.5 (d, 1H, *J* = 3.3 Hz, C(O)$\underline{C}H_2$CH), 40.5 (N$\underline{C}H_2CH_2$), 42.5 (d, *J* = 153.2 Hz, C(O)CH$_2\underline{C}$H), 61.7 (d, *J* = 6.3 Hz, $\underline{C}H_2CH_3$), 62.4 (d, *J* = 6.1 Hz, $\underline{C}H_2CH_3$), 89.9 (CH$_3\underline{C}$), 112.3 (Ar$\underline{C}$-H), 112.6 (Ar$\underline{C}$-quat), 119.1 (Ar$\underline{C}$-H), 119.2 (Ar$\underline{C}$-H), 121.8 (Ar$\underline{C}$-H), 123.6 (NH$\underline{C}$H), 128.0 (Ar$\underline{C}$-quat), 137.1 (Ar$\underline{C}$-quat), 173.1 (d, *J* = 15.9 Hz, CO); ***m/z* (ES$^+$)** 417 ([M+Na]$^+$, 35%), 811 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 417.1548 for $C_{19}H_{27}N_2O_5PNa^+$ [M+Na]$^+$, requires 417.1550.

7.4.4.3 Synthesis and characterisation of (±)-methyl 2-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxopyrrolidine-3-carboxylate (**4.107**)

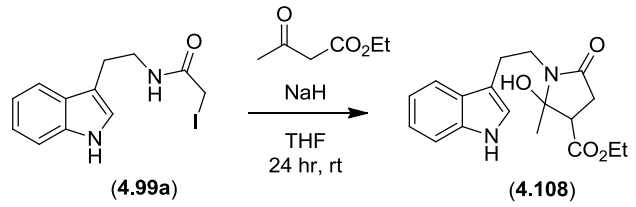


(**4.99a**) (**4.107**)

Following general procedure A (1.0 mmol scale of tryptamine derivative) the titled compound was obtained as a mixture of diastereomers (3 : 1) after 72 hours at room temperature as a colourless solid following trituration with ethyl acetate (178 mg, 56%).

M.P. 111-114 ^{o}C; **ν_{max}(film)/cm^{-1}** 3401 (br w, N-H, O-H), 1735 (s, C=O), 1676 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.60 (s, 3H, C$\underline{H}_3$C), 2.35 (dd, 1H, *J* = 16.5 Hz, *J* = 9.0 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.74-2.98 (m, 3H, C(O)CH$_A\underline{H}_B$CH, NCH$_2$C$\underline{H}_2$C), 3.13-3.43 (m, 3H, NC$\underline{H}_2$CH$_2$C, C(O)CH$_2$C$\underline{H}$ minor diastereomer for C(O)CH$_2$C$\underline{H}$ at 3.66-3.70 ppm), 3.66 (s, 3H, OC$\underline{H}_3$, minor diastereomer at 3.68 ppm), 6.06 (s, 1H, O-H, minor diastereomer at 6.37 ppm), 6.99 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.07 (t, 1H, *J* = 7.0 Hz, Ar-H), 7.18 (d, 1H, *J* = 2.0 Hz, NHC$\underline{H}$, minor diastereomer at 7.17 ppm), 7.34 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.57 (d, 1H, *J* = 7.6 Hz, Ar-H, minor diastereomer underneath), 10.84 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 25.9 (NCH$_2\underline{C}$H$_2$C), 26.9 (C$\underline{H}_3$C), 31.9 (C(O)C$\underline{H}_2$CH), 40.6 (NC$\underline{H}_2$CH$_2$C), 49.9 (C(O)CH$_2\underline{C}$H), 52.6 (OC$\underline{H}_3$), 89.8 (CH$_3\underline{C}$), 112.3 (Ar$\underline{C}$-H), 112.5 (Ar$\underline{C}$-quat), 119.1 (Ar$\underline{C}$-H), 119.2 (Ar$\underline{C}$-H), 121.8 (Ar$\underline{C}$-H), 123.6 (NH$\underline{C}$H), 128.0 (Ar$\underline{C}$-quat), 137.1 (Ar$\underline{C}$-quat), 171.0 (CO), 173.2 (CO); ***m/z* (ES$^+$)** 375 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 399.1309 for $C_{17}H_{20}N_2O_4Na^+$ [M+Na]$^+$, requires 339.1315.

7.4.4.4 Synthesis and characterisation of (±)-ethyl 2-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxopyrrolidine-3-carboxylate (**4.108**)



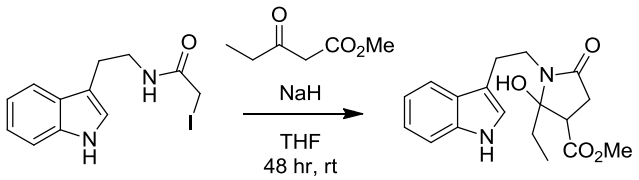
(**4.99a**) (**4.108**)

Following general procedure B (4.0 mmol scale of tryptamine derivative) the titled compound was obtained as a mixture of diastereomers (7 : 1) after 24 hours at room temperature as a colourless solid following flash silica gel chromatography (ethyl acetate : hexane, 1 : 1) (501 mg, 38%).

M.P. 145-149 **º**C; **ν_{max}(film)/cm^{-1}** 3339 (br w, N-H, O-H), 1731 (m, C=O), 1676 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.22 (t, 1H, *J* = 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.60 (s, 3H, C$\underline{H}_3$C), 2.34 (dd, 1H, *J* = 16.7 Hz, *J* = 9.1 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.75-2.99 (m, 3H, C(O)CH$_A\underline{H}_B$CH, C$\underline{H}_2$), 3.19 (app. t, 1H, *J* = 9.1 Hz, C(O)CH$_2$C$\underline{H}$), 3.25-3.44 (m, 2H, C$\underline{H}_2$), 4.07-4.17 (m, 2H, C$\underline{H}_2$CH$_3$), 6.04 (br s, 1H, O-H), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.07 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.18 (d, 1H, *J* = 1.7 Hz, NHC$\underline{H}$), 7.34 (d, 1H, *J*

= 8.1 Hz, Ar-H), 7.58 (d, 1H, *J* = 7.7 Hz, Ar-H), 10.83 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 15.0 ($\underline{C}H_3CH_2$), 25.9 ($\underline{C}H_2$), 26.8 ($\underline{C}H_3C$), 31.8 (C(O)$\underline{C}H_2$CH), 40.5 ($\underline{C}H_2$), 49.9 (C(O)$CH_2\underline{C}$H), 61.1 (O$\underline{C}H_2CH_3$), 89.8 ($CH_3\underline{C}$), 112.3 (Ar$\underline{C}$-H), 112.5 (Ar$\underline{C}$-quat), 119.1 (Ar$\underline{C}$-H), 119.2 (Ar$\underline{C}$-H), 121.8 (Ar$\underline{C}$-H), 123.6 (NH$\underline{C}$H), 128.0 (Ar$\underline{C}$-quat), 137.1 (Ar$\underline{C}$-quat), 170.5 (CO), 173.3 (CO); ***m/z* (ES$^+$)** 353 ([M+Na]$^+$, 30%), 683 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 353.1465 for $C_{18}H_{22}N_2O_4Na^+$ [M+Na]$^+$, requires 353.1472.

7.4.4.5 Synthesis and characterisation of (±)-methyl 2-ethyl-2-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-5-oxopyrrolidine-3-carboxylate (**4.109**)

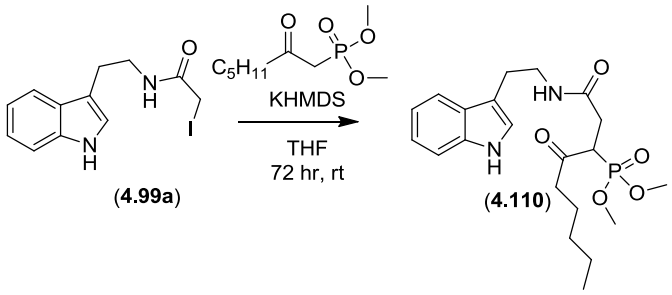


(**4.99a**) (**4.109**)

Following general procedure B (3.0 mmol scale of tryptamine derivative) the titled compound was obtained as a mixture of diastereomers (1 : 2) after 48 hours at room temperature as a colourless solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1:1) (429 mg, 43%).

M.P. 60-65 ºC; **ν_{max}(film)/cm^{-1}** 3366 (br w, N-H, O-H), 1733 (s, C=O), 1673 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 0.85 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$, minor diastereomer at 0.77 ppm), 1.85-1.96 (m, 1H, $C\underline{H}_AH_BCH_3$, minor diastereomer at 1.63-1.84 ppm), 1.99-2.09 (m, 1H, $CH_A\underline{H}_BCH_3$, minor diastereomer at 1.63-1.84 ppm), 2.38 (dd, 1H, *J* = 16.8 Hz, *J* = 9.3 Hz, C(O)C$\underline{H}_AH_B$CH), 2.75-3.02 (m, 3H, C(O)$CH_A\underline{H}_B$CH, C$\underline{H}_2$), 3.13-3.49 (m, 3H, C(O)CH_2C$\underline{H}$, C$\underline{H}_2$, minor diastereomer for C$\underline{H}_2$ at 2.52-2.65 ppm), 3.66 (s, 3H, C$\underline{H}_3$O, minor diastereomer at 3.69 ppm), 6.12 (s, 1H, O-H, minor diastereomer at 6.32 ppm), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.07 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.19 (s, 1H, NHC$\underline{H}$), 7.34 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.61 (d, 1H, *J* = 7.8 Hz, Ar-H, minor diastereomer at 7.54 ppm), 10.83 (br s, 1H, N-H, minor diastereomer at 10.88 ppm); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 9.3 ($CH_2\underline{C}H_3$), 25.2 ($\underline{C}H_2$, minor diastereomer at 25.8 ppm), 29.6 ($\underline{C}H_2$, minor diastereomer at 30.5 ppm), 32.2 ($\underline{C}H_2$, minor diastereomer at 33.7 ppm), 40.7 ($\underline{C}H_2$), 45.4 (C(O)$CH_2\underline{C}$H), 52.6 ($\underline{C}H_3$O, minor diastereomer at 52.8 ppm), 93.1 ($CH_2\underline{C}$), 112.3 (Ar$\underline{C}$-H), 112.5 (Ar$\underline{C}$-quat, minor diastereomer at 112.6 ppm), 119.2 (Ar$\underline{C}$-H), 121.8 (Ar$\underline{C}$-H), 123.5 (2C, NH$\underline{C}$H, Ar$\underline{C}$-H), 127.9 (Ar$\underline{C}$-quat), 137.1 (Ar$\underline{C}$-quat), 171.4 & 173.7 (2 x CO, minor diastereomers at 172.0 and 172.6 ppm); ***m/z* (ES$^+$)** 353 ([M+Na]$^+$, 30%), 683 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 353.1475 for $C_{18}H_{22}N_2O_4Na^+$ [M+Na]$^+$, requires 353.1472.

7.4.4.6 Synthesis and characterisation of (±)-dimethyl (1-{[2-(1*H*-indol-3-yl)ethyl]amino}-1,4-dioxononan-3-yl)phosphonate (**4.110**)

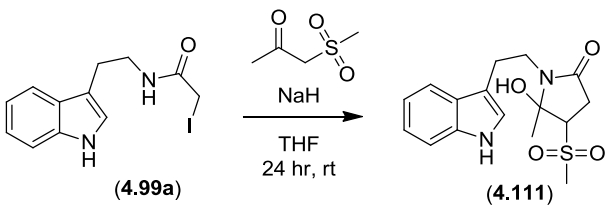


(**4.99a**) (**4.110**)

Following general procedure A (1.0 mmol scale of tryptamine derivative) the titled compound was obtained after 72 hours at room temperature as a clear oil following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (142 mg, 34%).

ν_{max}(film)/cm^{-1} 3282 (br w, N-H), 1735 (s, C=O), 1679 (s, C=O), 1237 (s, P-O, P=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.87 (t, 3H, *J* = 7.0 Hz, $C\underline{H}_3CH_2$), 1.27 (m, 4H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$), 1.58 (app. p, 2H, *J* = 7.5 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 2.51 (ddd, 1H, *J* = 16.0 Hz, *J* = 10.0 Hz, *J* = 3.0 Hz, $NHC(O)C\underline{H}_AH_BCH$), 2.66 (m, 1H, $C(O)C\underline{H}_AH_BCH_2$), 2.88 (m, 4H, $NHC(O)CH_A\underline{H}_BCH$, $C(O)CH_A\underline{H}_BCH_2$, $NHCH_2C\underline{H}_2C$), 3.51 (m, 2H, $NHC\underline{H}_2CH_2C$), 3.71 (s, 3H, $OC\underline{H}_3$), 3.74 (s, 3H, $OC\underline{H}_3$), 3.82 (ddd, 1H, *J* = 24.0 Hz, *J* = 11.0 Hz, *J* = 3.0 Hz, $NHC(O)CH_2C\underline{H}$), 5.91 (br s, 1H, $N\underline{H}CH_2CH_2C$), 6.99 (s, 1H, $NHC\underline{H}$), 7.11 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.19 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.36 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57 (d, 1H, *J* = 7.5 Hz, Ar-H), 8.52 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.9 ($\underline{C}H_3CH_2$), 22.4 ($\underline{C}H_2$), 23.0 ($CH_3CH_2CH_2\underline{C}H_2$), 25.1 ($NHCH_2\underline{C}H_2$), 31.0 ($\underline{C}H_2$), 32.7 ($NHC(O)\underline{C}H_2CH$), 39.9 ($NH\underline{C}H_2CH_2$), 44.1 ($C(O)\underline{C}H_2CH_2$), 47.2 (d, *J* = 137 Hz, $C(O)CH_2\underline{C}H$), 53.2 (d, *J* = 7 Hz, $O\underline{C}H_3$), 53.3 (d, *J* = 7 Hz, $O\underline{C}H_3$), 111.3 (Ar$\underline{C}$-H), 112.5 (Ar$\underline{C}$-quat), 118.6 (Ar$\underline{C}$-H), 119.3 (Ar$\underline{C}$-H), 122.0 (Ar$\underline{C}$-H), 122.3 ($NH\underline{C}H$), 127.2 (Ar$\underline{C}$-quat), 136.4 (Ar$\underline{C}$-quat), 169.7 (d, *J* = 17 Hz, CO), 205.2 (d, *J* = 4 Hz, CO); ***m/z* (ES$^+$)** 481 ($[M+MeCN+NH_4]^+$, 100%); **HRMS ES (+)** Found 445.1861 for $C_{21}H_{31}N_2O_5PNa^+$ $[M+Na]^+$, requires 445.1863.

7.4.4.7 Synthesis and characterisation of (±)-5-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-5-methyl-4-(methylsulfonyl)pyrrolidin-2-one (**4.111**)

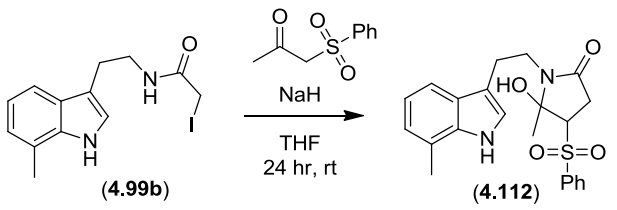


(**4.99a**) (**4.111**)

Following general procedure B (3.0 mmol scale of tryptamine derivative) the titled compound was obtained after 24 hours at room temperature as a pale yellow solid following trituration with ethyl acetate (622 mg, 62%).

M.P. 152-155 ºC; **ν_{max}(film)/cm^{-1}** 3398 (br w, N-H, O-H), 1667 (s, C=O), 1312 (s, S=O), 1277 (s, S=O), 1143 (s, S-O), 1130 (s, S-O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.65 (s, 3H, CC$\underline{H}_3$) 2.64 (dd, 1H, *J* = 16.6 Hz, *J* = 9.3 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.79-2.30 (m, 3H, C(O)CH$_A\underline{H}_B$CH, NCH$_2$C$\underline{H}_2$), 3.06 (s, 3H, SO$_2$C$\underline{H}_3$), 3.26-3.44 (m, 2H, NC$\underline{H}_2$CH$_2$), 3.94 (app. t, 1H, *J* = 9.3 Hz, C(O)CH$_2$C$\underline{H}$), 6.57 (s, 1H, O-H), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.08 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.20 (s, 1H, NHC$\underline{H}$), 7.35 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.85 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 25.8 (NCH$_2\underline{C}$H$_2$), 26.7 ($\underline{C}$H$_3$C), 31.5 (C(O)$\underline{C}$H$_2$CH), 40.4 (N$\underline{C}$H$_2$CH$_2$), 40.9 (SO$_2\underline{C}$H$_3$), 65.2 (C(O)CH$_2\underline{C}$H), 89.0 (CH$_3\underline{C}$), 112.3 (Ar$\underline{C}$-H), 112.4 (Ar$\underline{C}$-quat), 119.1 (Ar$\underline{C}$-H), 119.2 (Ar$\underline{C}$-H), 121.9 (Ar$\underline{C}$-H), 123.7 (NH$\underline{C}$H), 127.9 (Ar$\underline{C}$-quat),137.1 (Ar$\underline{C}$-quat), 171.1 (CO); ***m/z* (ES$^+$)** 359 ([M+Na]$^+$, 40%), 695 ([2M+Na]$^+$, 90%); **HRMS ES (+)** Found 359.1033 for $C_{16}H_{20}N_2O_4SNa^+$ [M+Na]$^+$, requires 359.1036.

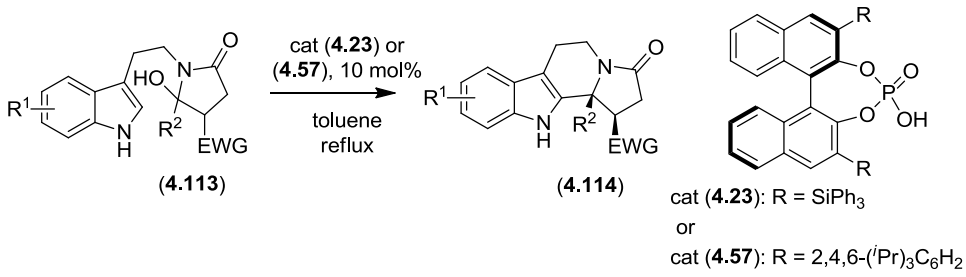
7.4.4.7 Synthesis and characterisation of (±)-5-hydroxy-5-methyl-1-[2-(7-methyl-1*H*-indol-3-yl)ethyl]-4-(phenylsulfonyl)pyrrolidin-2-one (**4.112**)



Following general procedure B (1.5 mmol scale of tryptamine derivative) the titled compound was obtained as a mixture of diastereomers (3 : 1) after 24 hours at room temperature as a white crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (552 mg, 89%).

M.P. 88-90 ^{o}C; **ν_{max}(film)/cm^{-1}** 3376 (br w, O-H, N-H), 1652 (C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.50 (s, 3H, C$\underline{H}_3$, minor diastereomer at 1.68 ppm), 2.43 (s, 3H, C$\underline{H}_3$), 2.56 (dd, 1H, *J* = 8.0 Hz, *J* = 2.5 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.71-2.97 (m, 3H, C(O)CH$_A\underline{H}_B$CH, NCH$_2$C$\underline{H}_2$C), 3.18-3.44 (m, 2H, NC$\underline{H}_2$CH$_2$C), 4.21 (t, 1H, *J* = 9.0 Hz, C(O)CH$_2$C$\underline{H}$ minor diastereomer at 4.12 ppm), 6.37 (s, 1H, O-H, minor distereomer at 6.64 ppm), 6.83-6.95 (m, 2H, 2 x Ar-H), 7.13-7.20 (m, 1H, NHC$\underline{H}$), 7.33-7.45 (m, 1H, Ar-H), 7.62-7.74 (m, 2H, Ar-H), 7.74-7.84 (m, 1H, Ar-H), 7.88-8.00 (m, 2H, 2 x Ar-H), 10.80 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 17.7 ($\underline{C}$H$_3$), 25.9 (NCH$_2\underline{C}$H$_2$C), 26.7 ($\underline{C}$H$_3$, diastereomer at 23.5 ppm), 31.6 (C(O)$\underline{C}$H$_2$CH), 40.2 (N$\underline{C}$H$_2$CH$_2$C), 65.9 (C(O)CH$_2\underline{C}$H, diastereomer at 67.7 ppm), 89.4 (CH$_3\underline{C}$, diastereomer at 90.1 ppm), 112.8 (Ar$\underline{C}$-quat), 116.7 (Ar$\underline{C}$-H), 119.4 (Ar$\underline{C}$-H), 121.4 (Ar$\underline{C}$-quat), 122.4 (Ar$\underline{C}$-H), 123.4 (NH$\underline{C}$H), 127.6 (Ar$\underline{C}$-quat), 129.0 (Ar$\underline{C}$-H), 129.8 (Ar$\underline{C}$-H), 130.0 (Ar$\underline{C}$-H), 130.5 (Ar$\underline{C}$-H), 134.8 (Ar$\underline{C}$-H), 136.6 (Ar$\underline{C}$-quat), 140.1 (Ar$\underline{C}$-quat), 170.7 (CO); ***m/z* (ES$^+$)** 471 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 435.1345 for $C_{22}H_{24}N_2O_4SNa^+$ [M+Na]$^+$, requires 435.1349.

7.4.5 Enantioselective and diastereoselective Pictet-Spengler reaction of aminols (**4.101**)-(**4.121**)

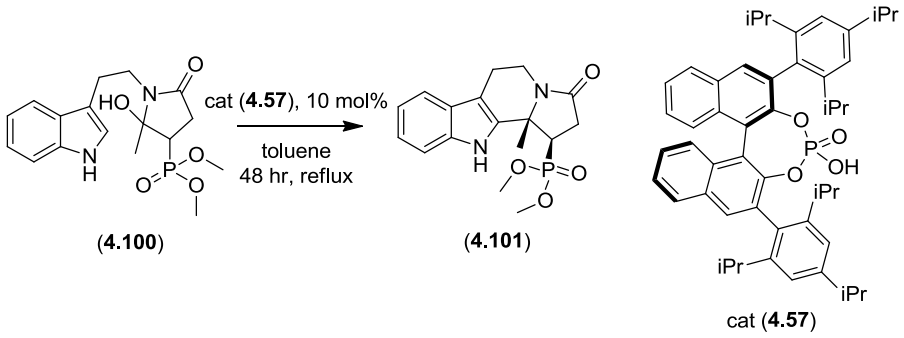


General procedure for the preparation of cyclised β-carbolines

To a solution of catalyst (**4.23**) or (**4.57**) (0.1 equivalents) in toluene (63 mL), at reflux, was added the solid hydroxylactam (**4.113**) (1 equivalent) and the solution was stirred under reflux for 24-72 hours. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate.

Note: All racemates were prepared using *para*-toluenesulfonic acid (catalytic amount) in refluxing toluene. Only one single diastereomer was obtained in all cyclization reactions.

7.4.5.1 Synthesis and characterisation of dimethyl ((1*R*,11b*S*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)phosphonate (**4.101**)

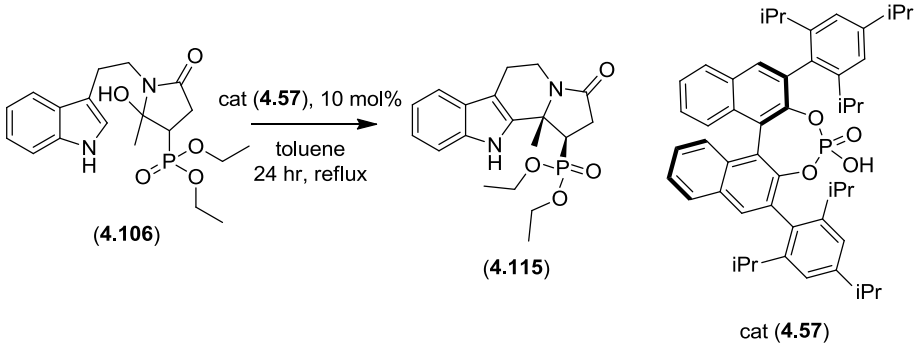


Following the general procedure (0.3 mmol scale) the titled compound was obtained after 48 hours at reflux in the presence of (**4.57**) as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (85 mg, 85%). The ee was determined by HPLC using a Chiralpak OJ column (60:40 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 6.9 min, minor t_R = 14.5 min (85% ee).

M.P. 174-177 ^{o}C; **$[\alpha]_D^{21}$** = + 31.9 (c = 0.92 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3300 (br w, N-H), 1696 (s, C=O), 1220 (s, P=O), 1033 (s, P-O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.63 (s, 3H, C$\underline{H}_3$C), 2.47-2.82 (m, 4H, NCH$_2$C$\underline{H}_2$C, C(O)C$\underline{H}_2$CH), 3.02 (ddd, 1H, *J* = 16.8 Hz, *J* = 12.2 Hz, *J* = 8.4 Hz,

C(O)CH_2C<u>H</u>), 3.11 (td, 1H, *J* = 12.5 Hz, *J* = 4.7 Hz, NC<u>H</u>$_A$H$_B$$CH_2$C), 3.73 (d, 3H, *J* = 10.9 Hz, OC<u>H</u>$_3$), 3.83 (d, 3H, *J* = 10.7 Hz, OC<u>H</u>$_3$), 4.23 (app. dd, 1H, *J* = 13.2 Hz, *J* = 6.2 Hz, NCH$_A$<u>H</u>$_B$$CH_2$C), 7.01 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.10 (m, 1H, *J* = 7.5 Hz, Ar-H), 7.43 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.45 (d, 1H, *J* = 8.1 Hz, Ar-H), 10.16 (br s, 1H, N-H); **^{13}C NMR: δ$_C$** (100 MHz, D_6-DMSO) 20.2 (NCH$_2$<u>C</u>H$_2$C), 21.1 (<u>C</u>H$_3$C), 31.1 (C(O)<u>C</u>H$_2$CH), 33.4 (N<u>C</u>H$_2$CH$_2$C), 39.7 (d, *J* = 34 Hz, C(O)CH$_2$<u>C</u>H), 52.3 (d, *J* = 7 Hz, O<u>C</u>H$_3$), 52.4 (d, *J* = 7 Hz, O<u>C</u>H$_3$), 58.7 (CH$_3$<u>C</u>), 104.8 (Ar<u>C</u>-quat), 111.2 (Ar<u>C</u>-H), 117.6 (Ar<u>C</u>-H), 118.4 (Ar<u>C</u>-H), 121.0 (Ar<u>C</u>-H), 125.5 (Ar<u>C</u>-quat), 134.9 (Ar<u>C</u>-quat), 136.6 (Ar<u>C</u>-quat), 166.2 (d, *J* = 18 Hz, CO); ***m/z* (ES$^+$)** 407 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 371.1131 for $C_{17}H_{21}N_2O_4PNa^+$ [M+Na]$^+$, requires 371.1131.

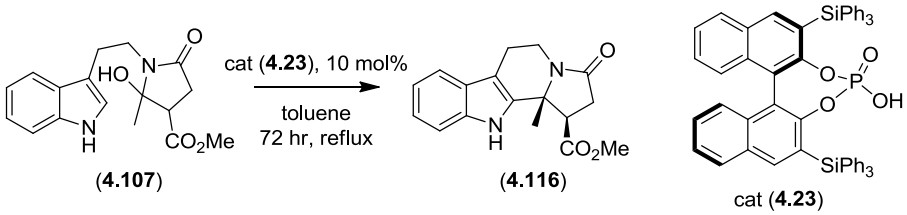
7.4.5.2 Synthesis and characterisation of diethyl ((1*R*,11b*S*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)phosphonate (**4.115**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 24 hours at reflux in the presence of (**4.57**) as a clear oil following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (106 mg, 94%). The ee was determined by HPLC using a Chiralpak AD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 9.1 min, minor t_R = 12.2 min (69% ee).

[α]$_D^{25}$ = + 45.6 (c = 0.91 in $CHCl_3$); **ν$_{max}$(film)/cm^{-1}** 3314 (br w, N-H), 1695 (s, C=O), 1217 (m, P=O), 1051 (s, P-O), 1023 (P-O); **^{1}H NMR: δ$_H$** (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* = 7.1 Hz, CH_2C<u>H</u>$_3$), 1.44 (t, 3H, *J* = 7.1 Hz, CH_2C<u>H</u>$_3$), 1.72 (s, 3H, C<u>H</u>$_3$C), 2.58-2.77 (m, 2H, C(O)C<u>H</u>$_A$H$_B$CH, C(O)CH$_2$C<u>H</u>), 2.79-2.94 (m, 3H, C(O)CH$_A$<u>H</u>$_B$CH, NCH$_2$C<u>H</u>$_2$), 3.06-3.16 (m, 1H, NC<u>H</u>$_A$H$_B$CH$_2$), 4.04-4.21 (m, 2H, P(O)C<u>H</u>$_2$CH$_3$), 4.22-4.37 (m, 2H, P(O)C<u>H</u>$_2$CH$_3$), 4.43-4.50 (m, 1H, NCH$_A$<u>H</u>$_B$CH$_2$), 7.10 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.18 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.40 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.48 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.00 (br s, 1H, N-H); **^{13}C NMR: δ$_C$** (100 MHz, $CDCl_3$) 16.4 (d, *J* = 2.1 Hz, P(O)CH_2<u>C</u>H$_3$), 16.5 (d, *J* = 1.8 Hz, P(O)CH_2<u>C</u>H$_3$), 21.2 (NCH$_2$<u>C</u>H$_2$), 21.8 (d, *J* = 1.7 Hz, <u>C</u>H$_3$C), 32.6 (d, *J* = 4.6 Hz, C(O)<u>C</u>H$_2$CH), 34.8 (N<u>C</u>H$_2$CH$_2$), 41.8 (d, *J* = 152.2 Hz, C(O)CH$_2$<u>C</u>H), 60.2 (d, *J* = 3.8 Hz, CH$_3$<u>C</u>), 62.5 (d, *J* = 7.2 Hz, P(O)<u>C</u>H$_2$CH$_3$), 62.8 (d, 1H, *J* = 6.3 Hz, P(O)<u>C</u>H$_2$CH$_3$), 105.8 (Ar<u>C</u>-quat), 111.7 (Ar<u>C</u>-H), 118.5 (Ar<u>C</u>-H), 119.5 (Ar<u>C</u>-H), 122.2 (Ar<u>C</u>-H), 126.3 (Ar<u>C</u>-quat), 136.0 (Ar<u>C</u>-quat), 136.8 (Ar<u>C</u>-quat), 169.6 (d, *J* = 17.6 Hz, CO); ***m/z* (ES$^-$)** 375 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 399.1444 for $C_{19}H_{25}N_2O_4PNa^+$ [M+Na]$^+$, requires 399.1444.

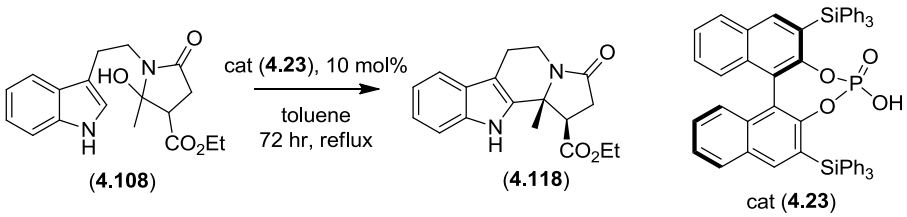
7.4.5.3 Synthesis and characterisation of methyl (1*R*,11b*R*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (**4.116**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 72 hours at reflux in the presence of (**4.23**) as a colourless solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (74 mg, 82%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 14.3 min, minor t_R = 22.1 min (92% ee).

M.P. 205-207 ^{o}C; **$[\alpha]_D^{21}$** = + 66.9 (c = 0.41 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3388 (br w, N-H), 1741 (s, C=O), 1678 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.48 (s, 3H, C$\underline{H_3}$C), 2.41-2.55 (m, 1H, C(O)C$\underline{H_A}$H$_B$CH), 2.62 (ddd, 1H, *J* = 15.5 Hz, *J* = 11.5 Hz, *J* = 6.0 Hz, NCH$_2$C$\underline{H_A}$H$_B$C), 2.74 (dd, 1H, *J* =15.5 Hz, *J* = 4.0 Hz, NCH$_2$CH$_A$$\underline{H_B}$C), 2.88 (dd, 1H, *J* = 16.5 Hz, *J* = 11.0 Hz, C(O)CH$_A$$\underline{H_B}$CH), 3.04 (td, 1H, *J* = 12.7 Hz, *J* = 4.5 Hz, NC$\underline{H_A}$H$_B$CH$_2$), 3.41 (dd, 1H, *J* = 11.0 Hz, *J* = 9.0 Hz, C(O)CH$_2$C$\underline{H}$), 3.85 (s, 3H, OC$\underline{H_3}$), 4.25 (dd, 1H, *J* = 12.7 Hz, *J* = 5.5 Hz, NCH$_A$$\underline{H_B}CH_2$), 7.00 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.10 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.42 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.48 (d, 1H, *J* = 8.1 Hz, Ar-H), 10.25 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 20.4 (NCH$_2$$\underline{C}H_2$C, $\underline{C}$H$_3$C), 32.2 (C(O)$\underline{C}$H$_2$CH), 34.0 (N$\underline{C}$H$_2$CH$_2$C), 47.6 (C(O)CH$_2$$\underline{C}$H), 52.0 (O$\underline{C}H_3$), 59.5 (CH$_3$$\underline{C}$), 105.5 (Ar$\underline{C}$-quat), 111.3 (Ar$\underline{C}$-H), 117.5 (Ar$\underline{C}$-H), 118.2 (Ar$\underline{C}$-H), 120.8 (Ar$\underline{C}$-H), 125.4 (Ar$\underline{C}$-quat), 135.4 (Ar$\underline{C}$-quat), 136.4 (Ar$\underline{C}$-quat), 168.9 (CO), 170.6 (CO); ***m/z* (ES$^+$)** 357 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 321.1206 for $C_{17}H_{18}N_2O_3Na^+$ [M+Na]$^+$, requires 321.1210.

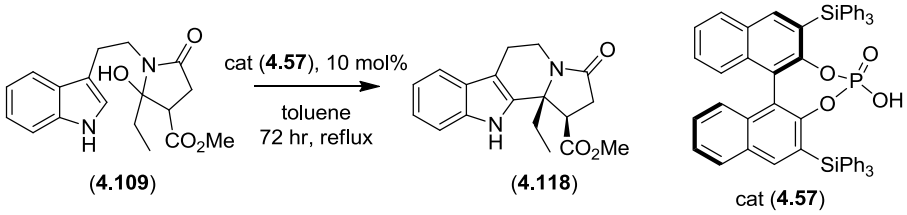
7.4.5.4 Synthesis and characterisation of ethyl (1R, 11bR)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (**4.118**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 72 hours at reflux in the presence of (**4.23**) as a colourless solid following flash silica gel chromatography (dichloromethane : acetone, 9.5 : 0.5) (79 mg, 85%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 10.6 min, minor t_R = 13.5 min (64% ee).

M.P. 137-142 ºC; **$[\alpha]_D^{25}$** = + 48.1 (c = 1.07 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3400 (br w, N-H), 1687 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.44 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 1.54 (s, 3H, $C\underline{H}_3C$), 2.68 (dd, 1H, *J* = 16.8 Hz, *J* = 8.8 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.83-2.87 (m, 2H, $NCH_2C\underline{H}_2$), 2.98-3.15 (m, 2H, C(O)CH$_A\underline{H}_B$CH, NC$\underline{H}_A$H$_B$CH$_2$), 3.34 (dd, 1H, *J* = 11.8 Hz, *J* = 8.8 Hz, C(O)CH$_2$C$\underline{H}$), 4.35-4.43 (m, 2H, $CH_3C\underline{H}_2$), 4.49-4.55 (m, 1H, NCH$_A\underline{H}_B$CH$_2$), 7.13 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.22 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.39 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.13 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.2 ($\underline{C}H_3CH_2$), 20.8 ($\underline{C}H_3C$), 21.1 ($NCH_2\underline{C}H_2$), 32.6 (C(O)$\underline{C}$H$_2$CH), 34.7 (N$\underline{C}$H$_2$CH$_2$), 49.1 (C(O)CH$_2\underline{C}$H), 60.1 ($CH_3\underline{C}$), 62.2 ($CH_3\underline{C}H_2$), 106.7 (Ar$\underline{C}$-quat), 111.3 (Ar$\underline{C}$-H), 118.6 (Ar$\underline{C}$-H), 119.7 (Ar$\underline{C}$-H), 122.4 (Ar$\underline{C}$-H), 126.4 (Ar$\underline{C}$-quat), 136.0 (Ar$\underline{C}$-quat), 136.5 (Ar$\underline{C}$-quat), 169.6 (CO), 171.5 (CO); ***m/z* (ES$^+$)** 335 ([M+Na]$^+$, 20%), 647 ([2M+Na]$^+$, 80%); **HRMS ES (+)** Found 335.1362 for $C_{18}H_{20}N_2O_3Na^+$ [M+Na]$^+$, requires 335.1366.

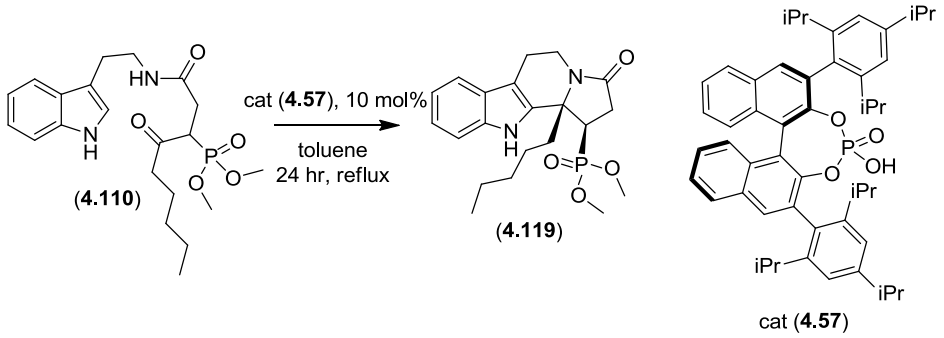
7.4.5.5 Synthesis and characterisation of methyl (1R, 11bR)-11b-ethyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (**4.118**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 72 hours at reflux in the presence of (**4.57**) as a colourless solid following flash silica gel chromatography (dichloromethane : acetone, 9 : 1) (79 mg, 84%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 13.2 min, minor t_R = 21.2 min (64% ee).

M.P. 169-172 ºC; **$[\alpha]_D^{25}$** = + 26.9 (c = 1.01 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3403 (w, N-H), 1719 (w, C=O), 1683 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.91 (app. t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$), 2.01 (dq, 1H, *J* = 15.1 Hz, *J* = 7.6 Hz, C$\underline{H}_A$H$_B$CH$_3$), 2.08-2.18 (m, 1H, CH$_A\underline{H}_B$CH$_3$), 2.65 (dd, 1H, *J* = 16.9 Hz, *J* = 9.4 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.83-2.87 (m, 2H, $NCH_2C\underline{H}_2$), 3.13 (m, 2H, C(O)CH$_A\underline{H}_B$CH, NC$\underline{H}_A$H$_B$CH$_2$), 3.40 (dd, 1H, J = 11.8 Hz, J = 9.4 Hz, C(O)CH$_2$C$\underline{H}$), 3.93 (s, 3H, OC$\underline{H}_3$), 4.57-4.62 (m, 1H, NCH$_A\underline{H}_B$CH$_2$), 7.13 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.21 (t, 1H, *J* = 7.1 Hz, Ar-H), 7.39 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.03 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 9.0 ($CH_2\underline{C}H_3$), 21.0 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 33.6 (C(O)$\underline{C}$H$_2$CH), 35.7 (N$\underline{C}$H$_2$CH$_2$), 48.6 (C(O)CH$_2\underline{C}$H), 52.9 (O$\underline{C}$H$_3$), 63.6 ($CH_2\underline{C}$N), 106.7 (Ar$\underline{C}$-quat), 111.3 (Ar$\underline{C}$-H), 118.6 (Ar$\underline{C}$-H), 119.7 (Ar$\underline{C}$-H), 122.3 (Ar$\underline{C}$-H), 126.5 (Ar$\underline{C}$-quat), 136.0 (Ar$\underline{C}$-quat), 136.2 (Ar$\underline{C}$-quat), 170.6 (CO), 172.1 (CO); ***m/z* (ES$^-$)** 311 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 335.1366 for $C_{18}H_{20}N_2O_3Na^+$ [M+Na]$^+$, requires 335.1366.

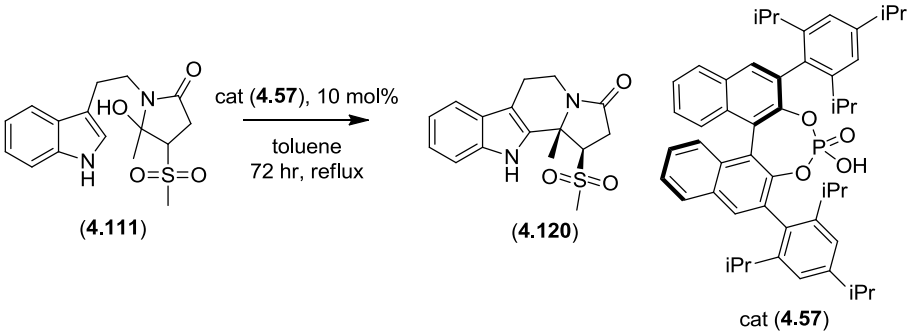
7.4.5.6 Synthesis and characterisation of dimethyl ((1*R*,11b*S*)-3-oxo-11b-pentyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)phosphonate (**4.119**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 48 hours at reflux in the presence of (**4.57**), as a yellow oil following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (80 mg, 66%). The ee was determined by HPLC using a Chiralpak AD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 9.1 min, minor t_R = 13.9 min (91% ee).

$[\alpha]_D^{21}$ = + 48.8 (c = 0.33 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3317 (br w, O-H), 1695 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.79-0.87 (m, 3H, $C\underline{H}_3CH_2$), 1.15-1.33 (m, 5H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$, $CH_3CH_2CH_2C\underline{H}_A\underline{H}_B$), 1.38-1.52 (m, 1H, $CH_3CH_2CH_2CH_A\underline{H}_B$), 2.12-2.27 (m, 2H, $CC\underline{H}_2CH_2CH_2$), 2.58 (dd, 1H, *J* = 16.0 Hz, *J* = 8.0 Hz, $C(O)C\underline{H}_A H_B CH$), 2.68-2.98 (m, 3H, $C(O)CH_A\underline{H}_B CH$, $NCH_2C\underline{H}_2C$), 3.14-3.25 (m, 1H, $NC\underline{H}_A H_B CH_2$), 3.76 (d, 3H, *J* = 11.0 Hz, $OC\underline{H}_3$), 3.93 (d, 3H, *J* = 11.0 Hz, $OC\underline{H}_3$), 4.57 (app. dd, 1H, *J* = 13.5 Hz, *J* = 6.5 Hz, $NCH_A\underline{H}_B CH_2$), 7.12 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, Ar-H), 7.20 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, Ar-H), 7.42 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.7 Hz, Ar-H), 9.88 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$,) 14.1 ($\underline{C}H_3CH_2$), 20.9 ($NCH_2\underline{C}H_2C$), 22.5 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 33.1 ($C(O)\underline{C}H_2CH$), 37.0 ($N\underline{C}H_2CH_2C$), 37.7 ($C\underline{C}H_2CH_2CH_2$), 42.4 (d, *J* = 152 Hz, $C(O)CH_2\underline{C}H$), 52.8 (d, *J* = 74 Hz, $O\underline{C}H_3$), 53.2 (d, *J* = 74 Hz, $O\underline{C}H_3$), 63.3 (d, *J* = 45 Hz, $CH_2\underline{C}N$), 106.5 (Ar$\underline{C}$-quat), 111.7 (Ar$\underline{C}$-H), 118.5 (Ar$\underline{C}$-H), 119.5 (Ar$\underline{C}$-H), 122.1 (Ar$\underline{C}$-H), 126.4 (Ar$\underline{C}$-quat), 135.6 (Ar$\underline{C}$-quat), 136.1 (Ar$\underline{C}$-quat), 170.6 (d, *J* = 180 Hz, CO); ***m/z* (ES$^+$)** 463 ($[M+MeCN+NH_4]^+$, 100%); **HRMS ES (+)** Found 427.1748 for $C_{21}H_{29}N_2O_4PNa^+$ $[M+Na]^+$, requires 427.1757.

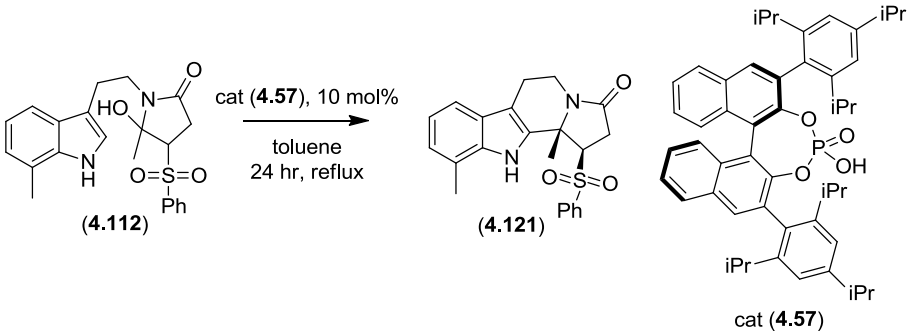
7.4.5.7 Synthesis and characterisation of (1*R*,11b*S*)-11b-methyl-1-(methylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.120**)



Following the general procedure (0.3 mmol scale) the titled compound was obtained after 72 hours at reflux in the presence of (**4.57**), as a colourless solid following flash silica gel chromatography (dichlorormethane : acetone, 9 : 1) (90 mg, 94%). The ee was determined by HPLC using a Chiralpak AD column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 9.7 min, minor t_R = 15.5 min (66% ee).

M.P. 127-130 ºC; **$[\alpha]_D^{25}$** = + 37.5 (c = 1.40 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3398 (br w, N-H), 1692 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.83 (s, 3H, $\underline{C}H_3C$), 2.68 (dd, 1H, *J* = 16.0 Hz, *J* = 8.5 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.78-2.85 (m, 2H, NCH$_2$C$\underline{H}_2$), 2.95 (s, 3H, SO$_2$C$\underline{H}_3$), 3.05-3.23 (m, 2H, C(O)CH$_A$$\underline{H}_BCH, NC\underline{H}_AH_BCH_2$), 3.75-3.84 (m, 1H, C(O)CH$_2$C$\underline{H}$), 4.41-4.50 (m, 1H, NCH$_A$$\underline{H}_BCH_2$), 7.08-7.19 (m, 2H, 2 x Ar-H), 7.32 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.48 (d, 1H, *J* = 7.2 Hz, Ar-H), 9.14 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 21.1 ($\underline{C}H_2$), 21.3 ($\underline{C}H_3C$), 33.4 ($\underline{C}H_2$), 34.8 (N$\underline{C}H_2CH_2$), 42.2 (SO$_2$$\underline{C}H_3$), 61.2 (CH$_3$$\underline{C}$), 64.4 (C(O)CH$_2$$\underline{C}$H), 107.1 (Ar$\underline{C}$-quat), 111.6 (Ar$\underline{C}$-H), 118.7 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 122.7 (Ar$\underline{C}$-H), 126.1 (Ar$\underline{C}$-quat), 134.9 (Ar$\underline{C}$-quat), 135.8 (Ar$\underline{C}$-quat), 166.9 (CO); ***m/z* (ES$^-$)** 317 ([M-H]$^-$, 70%); **HRMS ES (+)** Found 341.0931 for $C_{16}H_{18}N_2O_3SNa^+$ [M+Na]$^+$, requires 341.0930.

7.4.5.8 Synthesis and characterisation of (1*R*,11b*S*)-10,11b-dimethyl-1-(phenylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.121**)

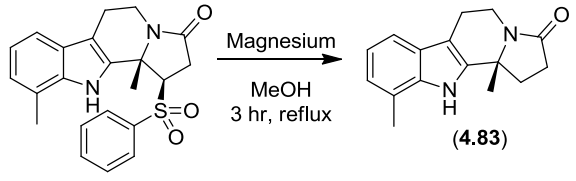


Following the general procedure (0.3 mmol scale) the titled compound was obtained after 24 hours at reflux in the presence of (**4.57**) as a colourless solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 3 : 2) (100 mg, 84%). The ee was determined by HPLC using a Chiralpak OD-H column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 14.3 min, major t_R = 17.1 min (72% ee).

M.P. 112-116 °C; **$[\alpha]_D^{21}$** = + 222.3 (c = 0.53 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3401 (br w, N-H), 1698 (s, C=O), 1148 (s, OMe); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.02 (s, 3H, C$\underline{H}_3$C), 2.41 (dd, 1H, *J* = 16.0 Hz, *J* = 8.0 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.61 (s, 3H, C$\underline{H}_3$C), 2.71-2.90 (m, 2H, NCH$_2$C$\underline{H}_2$C), 3.15 (ddd, 1H, *J* = 11.5 Hz, *J* = 4.5 Hz, *J* = 1.0 Hz, NC$\underline{H}_A$H$_B$CH$_2$C), 3.24 (ddd, 1H, *J* = 16.0 Hz, *J* = 12.0 Hz, *J* = 1.5 Hz, C(O)CH$_A$$\underline{H}_B$CH), 3.79 (dd, 1H, *J* = 12.0 Hz, *J* = 8.0 Hz, C(O)CH$_2$C$\underline{H}$), 4.48 (ddd, 1H, *J* = 13.0 Hz, *J* = 6.0 Hz, *J* = 1.0 Hz, NCH$_A$$\underline{H}_BCH_2$C), 7.05-7.13 (m, 2H, 2 x Ar-H indole), 7.36 (dd, 1H, *J* = 5.5 Hz, *J* = 3.0 Hz, Ar-H indole), 7.58-7.64 (m, 2H, 2 x Ar-H), 7.72 (tt, 1H, *J* = 8.0 Hz, 1.0 Hz, Ar-H), 7.87-7.93 (m, 2H, 2 x Ar-H), 9.42 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 16.7 (C$\underline{H}_3$C), 21.2 (NCH$_2$C$\underline{H}_2$C), 21.6 (C$\underline{H}_3$), 33.5 (C(O)C$\underline{H}_2$CH), 35.0 (NC$\underline{H}_2$CH$_2$C), 61.7 (CH$_3$C$\underline{N}$), 66.8 (C(O)CH$_2$C$\underline{H}$), 107.7 (Ar$\underline{C}$-quat), 116.4 (Ar$\underline{C}$-H indole), 120.2 (Ar$\underline{C}$-H indole), 120.9 (Ar$\underline{C}$-quat), 123.3 (Ar$\underline{C}$-H indole), 125.7 (Ar$\underline{C}$-quat), 128.1 (2 x Ar$\underline{C}$-H), 129.8 (2 x Ar$\underline{C}$-H), 134.7 (Ar$\underline{C}$-H), 134.8 (Ar$\underline{C}$-quat), 135.6 (Ar$\underline{C}$-quat), 138.7 (Ar$\underline{C}$-quat), 167.0 (CO); ***m/z* (ES$^+$)** 453 ([M+MeCN+NH$_4$]$^+$, 65%); **HRMS ES (+)** Found 417.1234 for $C_{22}H_{22}N_2O_3SNa^+$ [M+Na]$^+$, requires 417.1243.

7.4.6 Proof of (1*R*,11b*S*) configuration of (**4.121**)

7.4.6.1 Synthesis and characterisation of (11b*R*)-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.83**)[109]



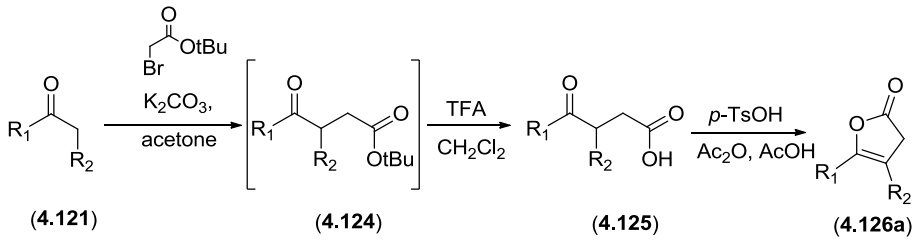
(**4.121**) (**4.83**)

To a solution of (**4.121**) (54 mg, 0.136 mmol) in anhydrous MeOH (15 mL) under N_2 were added magnesium turnings (108 mg, 4.46 mmol) and the solution was heated to 50 °C before cooling to room temperature and stirring for 40 minutes. The solution was then brought to reflux for 3 hours before cooling to room temperature and pouring onto 2M aqueous HCl (20 mL). The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by chromatography on silica gel eluting with ethyl acetate to yield the titled product as a colourless solid (17mg, 48%). The ee was determined by HPLC using a Chiralpak OD column (90:10 hexane/isopropanol) flow rate 1.5 ml/min, 220 nm, major t_R = 10.6 min, minor t_R = 13.9 min (72% ee).

M.P. 175-180 ºC (lit.[78] 194-197 ºC); $[\alpha]_D^{21}$ = + 176.7 (c = 1.25 in $CHCl_3$) (lit. $[\alpha]_D^{21}$ = + 215.6 (c = 1.25 in $CHCl_3$), 92% ee); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.64 (s, 3H, C$\underline{H}_3$), 2.17-2.27 (m, 1H, C(O)CH_2C$\underline{H}_A\underline{H}_B$), 2.32-2.39 (m, 1H, C(O)CH_2C$H_A\underline{H}_B$), 2.46-2.49 (m, 1H, C(O)C$\underline{H}_A$H$_B$CH_2), 2.51 (s, 3H, C$\underline{H}_3$), 2.66-2.74 (m, 1H, C(O)C$H_A\underline{H}_B$CH_2), 2.77-2.90 (m, 2H, NCH_2C$\underline{H}_2$C), 3.07-3.15 (m, 1H, NC$\underline{H}_A$H$_B$CH_2C), 4.46-4.51 (m, 1H, NC$H_A\underline{H}_B$CH_2C), 7.01 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.07 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.35 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.01 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 16.8 (C$\underline{H}_3$), 21.3 (NCH_2C$\underline{H}_2$C), 25.5 (C$\underline{H}_3$), 30.7 (C(O)CH_2C$\underline{H}_2$), 32.9 (C(O)C$\underline{H}_2$CH_2), 35.0 (NC$\underline{H}_2$CH_2C), 59.6 (CH_3C$\underline{N}$), 107.5 (Ar$\underline{C}$-quat),116.2 (Ar$\underline{C}$-H), 120.1 (Ar$\underline{C}$-H), 120.2 (Ar$\underline{C}$-quat), 122.9 (Ar$\underline{C}$-H), 126.3 (Ar$\underline{C}$-quat), 135.6 (Ar$\underline{C}$-quat), 137.4 (Ar$\underline{C}$-quat), 172.7 (CO); ***m/z* (ES$^+$)** 313 ($[M+MeCN+NH_4]^+$, 95%).

The HPLC retention times and the specific rotation confirmed the (*R*) configuration at the quaternary center hence confirming the (1*R*,11b*S*) configuration of (**4.121**). The configurations of the other cyclized products (**4.101**)-(**4.120**) were assigned by analogy.

7.4.7 Preparation of enol lactones (**4.131**)-(**4.134**)

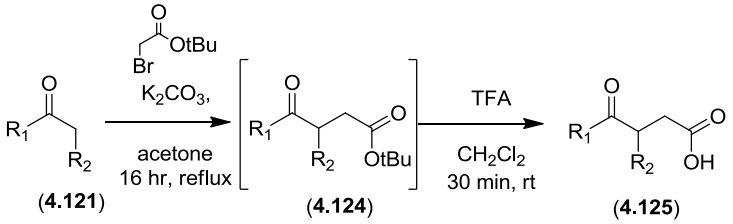


(**4.121**) (**4.124**) (**4.125**) (**4.126a**)

Entry	Compound no.	R_1	R_2	Yield of oxoacid (**4.125**)	Yield of enol lactone (**4.126a**)
1	(**4.131**)	Me	CO_2Me	40%	74%
2	(**4.132**)	Me	$P(O)(OMe)_2$	46%	64%
3	(**4.133**)	n-pentyl	$P(O)(OMe)_2$	65%	41%
4	(**4.134**)	Me	SO_2Ph	57%*	15%$^{\Psi}$

* Yield of isolated *t*-butyl oxoester. $^{\Psi}$Yield of enol lactone from *t*-butyl oxoester.

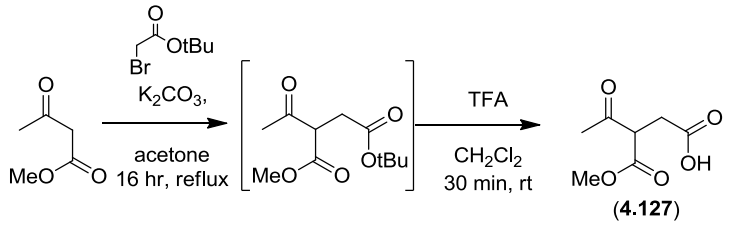
7.4.7.1 Preparation of 4-oxo carboxylic acids



General procedure for the preparation of 4-oxo carboxylic acids

To a solution of ketone (1 equivalent) in acetone (3 mL per 1 mmol of ketone) was added anhydrous K_2CO_3 (5 equivalents) followed by *tert*-butyl bromoacetate (1 equivalent). The heterogeneous mixture was heated to reflux for 16 hours. It was allowed to cool to room temperature and water was added (volume identical to acetone). The solution was extracted with diethyl ether (3 x volume of water added). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude *tert*-butyl 4-oxo carboxylate (for R_2 = $PhSO_2$, the *tert*-butyl ester was isolated and purified and the dehydrative cyclisation to the enol lactone was carried out on the corresponding crude 4-oxo carboxylic acid). The crude *tert*-butyl oxo ester mixture was dissolved in CH_2Cl_2 (3 mL per 1 g of mixture) and TFA was added. The solution was stirred at room temperature for 30 minutes and the solvents were removed under a nitrogen flow. The residue was purified by chromatography on silica gel to afford the title compound.

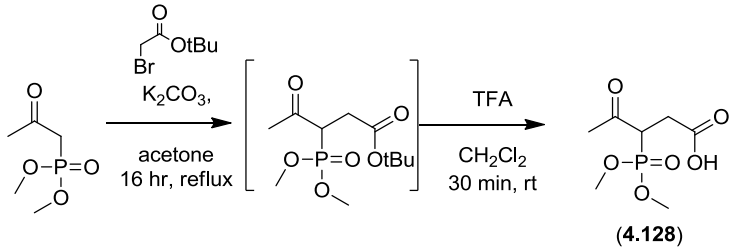
7.4.7.1.1 Synthesis and characterisation of (±)-3-(methoxycarbonyl)-4-oxopentanoic acid (**4.127**)



Following the general procedure (5g, 43 mmol scale of methyl acetoacetate) the titled compound was obtained as a colourless solid (2.98 g, 40% over 2 steps) following flash silica gel chromatography (dichloromethane : ethyl acetate, 9 : 1 to 4 : 1).

M.P. 46-49 ^{o}C; **ν_{max}(film)/cm^{-1}** 3209 (br w, O-H), 1739 (s, C=O), 1718 (s, C=O), 1270 (s, C-O), 1163 (s, C-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.35 (s, 3H, $C\underline{H}_3C(O)$), 2.88 (dd, 1H, *J* = 8.0 Hz, *J* = 6.5 Hz, $C\underline{H}_A H_B CO_2H$), 3.03 (dd, 1H, *J* = 18.0 Hz, *J* = 8.0 Hz, $CH_A\underline{H}_B CO_2H$), 3.76 (s, 3H, $OC\underline{H}_3$), 3.96 (app. t, 1H, *J* = 7.0 Hz, $C\underline{H}CH_2CO_2H$), 10.19 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 29.9 ($\underline{C}H_3C(O)$), 32.0 ($CH\underline{C}H_2CO_2H$), 52.9 ($O\underline{C}H_3$), 54.1 ($\underline{C}HCH_2CO_2H$), 168.6 (CO), 177.1 (CO), 201.4 (CO); ***m/z* (ES$^+$)** 197 ([M+Na]$^+$, 50%), 387 ([2M+K]$^+$, 100%); **HRMS ES (+)** Found 197.0413 for $C_7H_{10}O_5Na^+$ [M+Na]$^+$, requires 197.0420.

7.4.7.1.2 Synthesis and characterisation of (±)-3-(dimethoxyphosphoryl)-4-oxopentanoic acid (**4.128**)

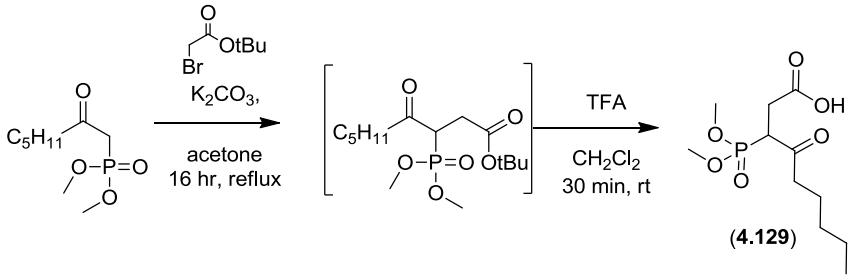


(**4.128**)

Following the general procedure (1.5 g, 9 mmol scale of dimethyl (2-oxopropyl)phosphonate) the titled compound was obtained as a colourless solid (415 mg, 46% over 2 steps) following flash silica gel chromatography (dichloromethane : ethyl acetate, 3 : 2).

M.P. 97-100 ^{o}C; **ν_{max}(film)/cm^{-1}** 3412 (br w, O-H), 1792 (s, C=O), 1720 (s, C=O), 1238 (s, P=O), 1209 (s, C-O / P-O), 1052 (s, C-O / P-O), 1033 (s, C-O / P-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.40 (s, 3H, $C\underline{H}_3C(O)$), 2.73 (ddd, 1H, *J* = 18.0 Hz, *J* = 9.5 Hz, *J* = 3.0 Hz, $CHC\underline{H}_A\underline{H}_BCO_2H$), 3.16 (ddd, 1H, *J* = 18.0 Hz, *J* = 11.0 Hz, *J* = 7.5 Hz, $CHCH_A\underline{H}_BCO_2H$), 3.72 (ddd, 1H, *J* = 25.0 Hz, *J* = 11.0 Hz, *J* = 3.0 Hz, $C\underline{H}CH_2CO_2H$), 3.77 (d, 3H, *J* = 2.0 Hz, $OC\underline{H}_3$), 3.80 (d, 3H, *J* = 2.0 Hz, $OC\underline{H}_3$), 9.44 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 30.8 (d, *J* = 3 Hz, $CH\underline{C}H_2CO_2H$), 31.2 ($\underline{C}H_3C(O)$), 47.7 (d, *J* = 127 Hz, $\underline{C}HCH_2CO_2H$), 53.5 (d, *J* = 7 Hz, $O\underline{C}H_3$), 53.8 (d, *J* = 7 Hz, $O\underline{C}H_3$), 175.0 (d, *J* = 19 Hz, CO), 199.8 (d, *J* = 5 Hz, CO); ***m/z* (ES$^-$)** 223 ([M-H]$^-$, 80%), 469 ([2(M-H)+K]$^-$, 100%); **HRMS ES (+)** Found 247.0344 for $C_7H_{13}O_6PNa^+$ [M+Na]$^+$, requires 247.0342.

7.4.7.1.3 Synthesis and characterisation of (±)-3-(dimethoxyphosphoryl)-4-oxononanoic acid (**4.129**)



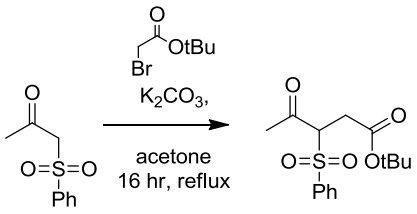
(**4.129**)

Following the general procedure (1.03 mL, 5 mmol scale of dimethyl (2-oxoheptyl)phosphonate) the titled compound was obtained as a colourless oil (922 mg, 65% over 2 steps) following flash silica gel chromatography (dichloromethane : ethyl acetate, 9 : 1).

ν_{max}(film)/cm^{-1} 3413 (br s, O-H), 1719 (s, C=O), 1238 (s, P=O), 1034 (s, C-O/P-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.89 (t, 3H, *J* = 7.0 Hz, $C\underline{H}_3CH_2$), 1.20-1.40 (m, 4H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$), 1.60 (p, 2H, *J* = 7.0 Hz, $C(O)CH_2C\underline{H}_2$), 2.63 (dt, 1H, *J* = 18.0 Hz, *J* = 7.0 Hz, $C(O)C\underline{H}_A\underline{H}_BCH_2$), 2.75 (ddd, 1H, *J* = 18.0 Hz, *J* = 9.5 Hz, *J* = 3.0 Hz, $CHC\underline{H}_A\underline{H}_BCO_2H$), 2.85 (dt, 1H, *J* = 18.0 Hz, *J* = 7.5 Hz, $C(O)CH_A\underline{H}_BCH_2$), 3.20 (ddd, 1H, *J* = 18.0 Hz, *J* = 11.0 Hz, *J* = 7.5 Hz, $CHCH_A\underline{H}_BCO_2H$), 3.69 (ddd, 1H, *J* = 11.0 Hz, *J* = 25.0 Hz, *J* = 3.0 Hz, $C\underline{H}CH_2CO_2H$), 3.77 (s, 3H, $OC\underline{H}_3$), 3.79 (s, 3H, $OC\underline{H}_3$),

7.57 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.9 ($\underline{C}H_3CH_2$), 22.4 ($CH_3\underline{C}H_2$), 23.0 ($C(O)CH_2\underline{C}H_2$), 30.8 ($CH\underline{C}H_2CO_2H$), 31.0 ($CH_3CH_2\underline{C}H_2$), 43.9 ($C(O)\underline{C}H_2CH_2$), 47.2 (d, *J* = 128 Hz, $\underline{C}HCH_2CO_2H$), 53.4 (d, *J* = 7 Hz, $O\underline{C}H_3$), 53.7 (d, *J* = 7 Hz, $O\underline{C}H_3$), 175.2 (d, *J* = 19 Hz, CO), 204.2 (d, *J* = 5 Hz, CO); ***m/z* (ES$^+$)** 279 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 303.0969 for $C_{11}H_{21}O_6PNa^+$ $[M+Na]^+$, requires 303.0968.

7.4.7.1.4 Synthesis and characterisation of (±)-*tert*-butyl 4-oxo-3-(phenylsulfonyl)pentanoate (**4.130**)

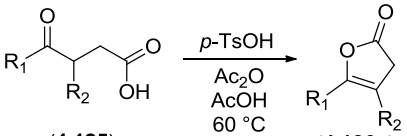


(**4.130**)

Following the general procedure (991 mg , 5 mmol scale of dimethyl 1-(phenylsulfonyl)acetone) the titled compound was obtained as a colourless solid (891 mg, 57%) following flash silica gel chromatography (petroleum ether : ethyl acetate, 9 : 1).

M.P. 116-118 ^oC; **ν_{max}(film)/cm^{-1}** 1724 (s, C=O), 1322 (s, S=O), 1149 (s, S=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.38 (s, 9H, $C(C\underline{H}_3)_3$), 2.52 (s, 3H, $C\underline{H}_3C(O)$), 2.85 (m, 2H, $C(O)C\underline{H}_2CH$), 4.58 (dd, 1H, *J* = 11.5 Hz, *J* = 3.5 Hz, $C(O)CH_2C\underline{H}$), 7.59 (t, 2H, *J* = 7.5 Hz, 2 x Ar-H), 7.71 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.78 (d, 2H, *J* = 7.5 Hz, 2 x Ar-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 27.9 ($C(\underline{C}H_3)_3$), 32.2 ($\underline{C}H_3C(O)$), 33.5 ($C(O)\underline{C}H_2CH$), 70.7 ($C(O)CH_2\underline{C}H$), 82.4 ($\underline{C}(CH_3)_3$), 129.3 (2 x Ar$\underline{C}$-H), 129.4 (2 x Ar$\underline{C}$-H), 134.6 (Ar$\underline{C}$-H), 135.9 (Ar$\underline{C}$-quat), 168.7 (CO), 199.0 (CO); ***m/z* (ES$^+$)** 335 ($[M+Na]^+$, 50%), 647 ($[2M+Na]^+$, 100%); **HRMS ES (+)** Found 335.0917 for $C_{15}H_{20}O_5SNa^+$ $[M+Na]^+$, requires 335.0924.

7.4.7.2 Preparation of enol lactones

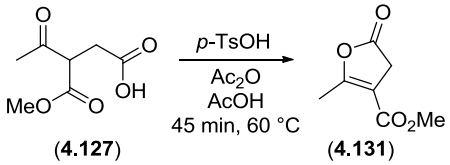


(**4.125**) (**4.126a**)

General procedure for the preparation of enol lactones

To a solution of 4-oxo carboxylic acid (1 equivalent) in acetic anhydride (1 mL per 0.5 mmol of substrate) and acetic acid (1 mL per 0.5 mmol of substrate) was added *p*-TsOH (0.1 equivalents) and the solution was heated to 60 °C for 45 minutes to 5 hours (completion followed by TLC) and allowed to cool to room temperature. Water was added (10 mL per 1 mmol of starting material). The solution was extracted with ethyl acetate (3 x 20 mL per 1 mmol of starting material). The combined organic layers were dried over Na_2SO_4 and the solvent concentrated *in vacuo*. The product was purified by chromatography on silica gel.

7.4.7.2.1 Synthesis and characterisation of methyl 2-methyl-5-oxo-4,5-dihydrofuran-3-carboxylate (**4.131**)

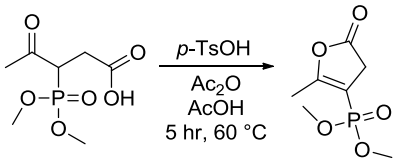


(**4.127**) (**4.131**)

Following the general procedure (4.05 mmol scale of oxoacid) the titled compound was obtained after heating at 60 °C for 45 minutes as a colourless crystalline solid (469 mg, 74%) following flash silica gel chromatography (dichloromethane).

M.P. 61-63 ^{o}C; **ν_{max}(film)/cm^{-1}** 1807 (s, C=O lactone), 1713 (s, C=O ester); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.41 (t, 3H, *J* = 2.5 Hz, C$\underline{H}_3$C), 3.45 (m, 2H, C(O)C$\underline{H}_2$), 3.78 (s, 3H, OC$\underline{H}_3$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.8 (C$\underline{H}_3$C), 33.6 (C(O)C$\underline{H}_2$), 51.6 (OC$\underline{H}_3$), 105.9 (C-quat), 163.5 & 163.7 (C-quat, CO), 172.8 (CO); **HRMS CI (+)** Found 174.0767 (100%) for $C_7H_{12}NO_4^+$ $[M+NH_4]^+$, requires 174.0761.

7.4.7.2.2 Synthesis and characterisation of dimethyl (2-methyl-5-oxo-4,5-dihydrofuran-3-yl)phosphonae (**4.132**)

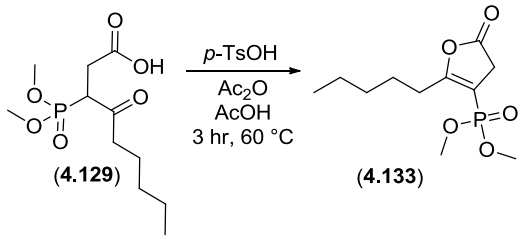


(**4.128**) (**4.132**)

Following the general procedure (1.44 mmol scale of oxoacid) the titled compound was obtained after heating at 60 °C for 5 hours as a colourless oil (191 mg, 64%) following flash silica gel chromatography (dichloromethane : acetone, 4 : 1).

ν_{max}(film)/cm^{-1} 1816 (s, C=O), 1238 (s, P=O), 1034 (s, C-O/P-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.32 (m, 3H, C$\underline{H}_3$C), 3.30 (m, 2H, C(O)C$\underline{H}_2$), 3.73 (s, 3H, OC$\underline{H}_3$), 3.76 (s, 3H, OC$\underline{H}_3$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.8 (C$\underline{H}_3$C), 34.9 (d, *J* = 9.0 Hz, C(O)C$\underline{H}_2$), 52.4 (2 x OC$\underline{H}_3$), 99.1 (d, *J* = 220 Hz, C-quat), 165.0 (d, *J* = 25 Hz, C-quat), 173.6 (d, *J* = 18 Hz, CO); ***m/z* (ES$^+$)** 229 ($[M+Na]^+$, 40%), 435 ($[2M+Na]^+$, 90%); **HRMS ES (+)** Found 229.0239 for $C_7H_{11}O_5PNa^+$ $[M+Na]^+$, requires 229.0236.

7.4.7.2.3 Synthesis and characterisation of dimethyl (5-oxo-2-pentyl-4,5-dihydrofuran-3-yl)phosphonate (**4.133**)

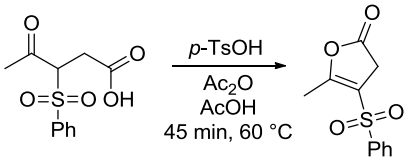


(**4.129**) (**4.133**)

Following the general procedure (0.58 mmol scale of oxoacid) the titled compound was obtained after heating at 60 °C for 3 hours as a colourless oil (63 mg, 41%) following flash silica gel chromatography (dichloromethane : acetone, 9 : 1).

ν_{max}(film)/cm^{-1} 1814 (s, C=O), 1235 (s, P=O), 1030 (s, C-O/P-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.89 (t, 3H, *J* = 7.0 Hz, C$\underline{H}_3$CH$_2$), 1.33 (m, 4H, CH$_3$C$\underline{H}_2$, CH$_3$CH$_2$C$\underline{H}_2$), 1.61 (p, 2H, *J* = 7.5 Hz, CCH$_2$C$\underline{H}_2$), 2.71 (m, 2H, CC$\underline{H}_2$CH$_2$), 3.31 (m, 2H, C(O)C$\underline{H}_2$C), 3.73 (s, 1H, 3H, OC$\underline{H}_3$), 3.76 (s, 3H, OC$\underline{H}_3$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.9 (C$\underline{H}_3$CH$_2$), 22.2 (CH$_3$C$\underline{H}_2$), 26.3 (d, *J* = 2 Hz, CCH$_2$C$\underline{H}_2$), 27.5 (CC$\underline{H}_2$CH$_2$), 31.1 (CH$_3$CH$_2$C$\underline{H}_2$), 34.9 (d, *J* = 9 Hz, C(O)C$\underline{H}_2$C), 52.4 (2 x OC$\underline{H}_3$), 98.8 (d, *J* = 221 Hz, C-quat), 168.7 (d, *J* = 26 Hz, C-quat), 173.9 (d, *J* = 18 Hz, CO); ***m/z* (ES$^+$)** 285 ([M+Na]$^+$, 40%); **HRMS ES (+)** Found 285.0860 for $C_{11}H_{19}O_5PNa^+$ [M+Na]$^+$, requires 285.0862.

7.4.7.2.4 Synthesis and characterisation of 5-methyl-4-(phenylsulfonyl)furan-2(3*H*)-one (**4.134**)



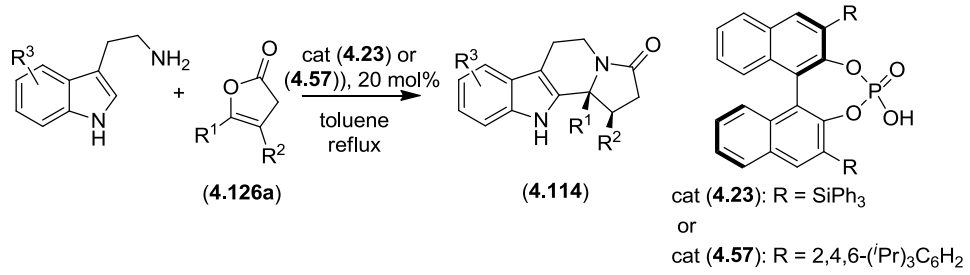
crude (**4.130b**) (**4.134**)

Following the general procedure (1.56 mmol scale of *tert*-butyl oxoester) the titled compound was obtained after heating at 60 °C for 45 minutes as a colourless solid (56 mg, 15% over 2 steps) following flash silica gel chromatography (increasing polarity from petroleum ether : ethyl acetate, 4 : 1 to 3 : 2).

M.P. 102-105 ^{o}C; **ν_{max}(film)/cm^{-1}** 1821 (s, C=O), 1319 (s, S=O), 1165 (s, S=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.48 (t, 3H, *J* = 2.5 Hz, C$\underline{H}_3$C), 3.36-3.41 (m, 2H, C(O)C$\underline{H}_2$C), 7.59 (t, 2H, *J* = 7.5 Hz, 2 x Ar-H), 7.68 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.88 (d, 2H, *J* = 7.5 Hz, 2 x Ar-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.0 (C$\underline{H}_3$C), 33.8 (C(O)C$\underline{H}_2$C), 114.3 (C-quat), 127.2 (2 x ArC-H), 129.7 (2 x ArC-H), 134.0

(ArC-H), 140.3 (C-quat), 161.4 (C-quat), 170.3 (CO); ***m/z* (ES$^+$)** 293 ([M+MeOH+Na]$^+$, 60%); **HRMS ES (+)** Found 293.0465 for $C_{12}H_{14}O_5SNa^+$ [M+MeOH+Na]$^+$, requires 293.0454.

7.4.8 Preparation of cyclised β-carbolines from enol lactones

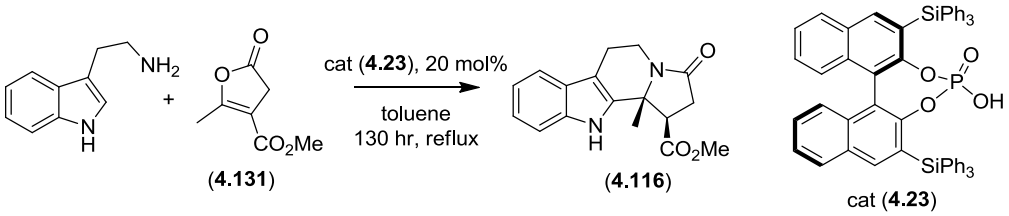


General procedure for the preparation of cyclized β-carbolines from enol lactones

Enol lactone (**4.126a**) (0.2 mmol, 1 equivalent) was dissolved in toluene (42 mL) and a tryptamine derivative (0.2 mmol, 1 equivalent) was added in one portion at room temperature, immediately followed by the addition of phosphoric acid catalyst (**4.23**) or (**4.57**) (0.02 mmol, 0.1 equivalents) in one portion. The resulting suspension was heated under reflux for 34 hours. Another portion of catalyst (**4.23**) or (**4.57**) (0.02 mmol, 0.1 equivalents) was then added to the hot mixture, and the solution was heated under reflux for 2 to 6 days (48 to 144 hours). The solvent was removed *in vacuo*, and the residue purified by chromatography on silica gel (see below for eluent systems).

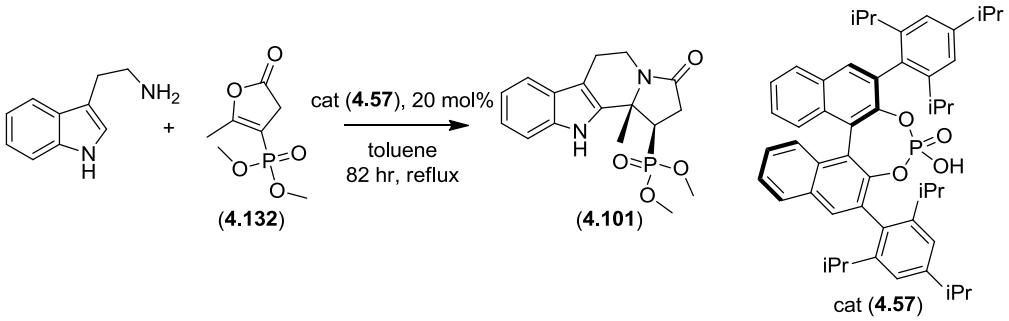
Note: All racemates were prepared using *para*-toluenesulfonic acid (catalytic amount) in refluxing toluene. A single diastereomer was obtained in all cyclization reactions.

7.4.8.1 Synthesis and characterisation of methyl (1*R*,11b*R*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (**4.116**)



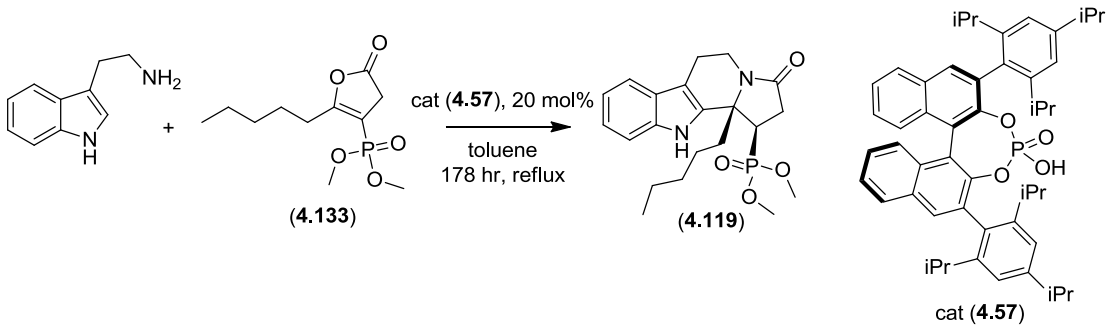
Following the general procedure the titled compound was obtained after 34 + 96 hours at reflux in the presence of (**4.23**) as a colourless crystalline solid following flash silica chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (44 mg, 74%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 12.3 min, minor t_R = 18.9 min (75% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.3**).

7.4.8.2 Synthesis and characterisation of dimethyl ((1*R*,11b*S*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)phosphonate (**4.101**)



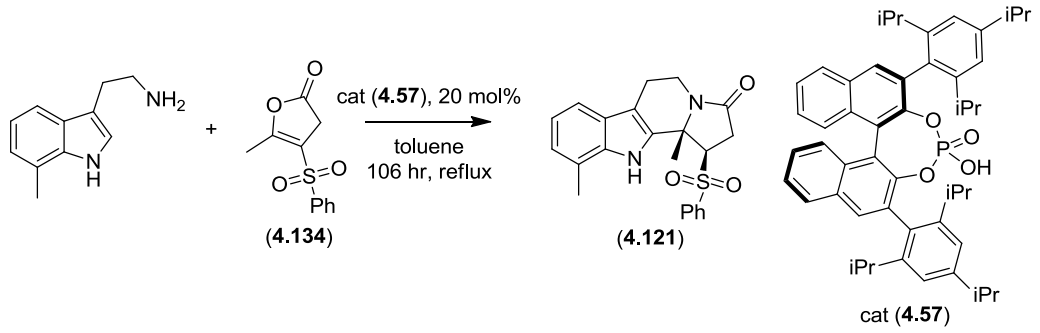
Following the general procedure the titled compound was obtained after 34 + 48 hours at reflux in the presence of (**4.57**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (63 mg, 95%). The ee was determined by HPLC using a Chiralpak OJ column (60:40 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 6.9 min, minor t_R = 14.5 min (85% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.1**).

7.4.8.3 Synthesis and characterisation of dimethyl ((1*R*,11b*S*)-3-oxo-11b-pentyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)phosphonate (**4.119**)



Following the general procedure the titled compound was obtained after 34 + 144 hours at reflux in the presence of (**4.57**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (73 mg, 90%). The ee was determined by HPLC using a Chiralpak AD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 9.1 min, minor t_R = 13.9 min (91% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.6**).

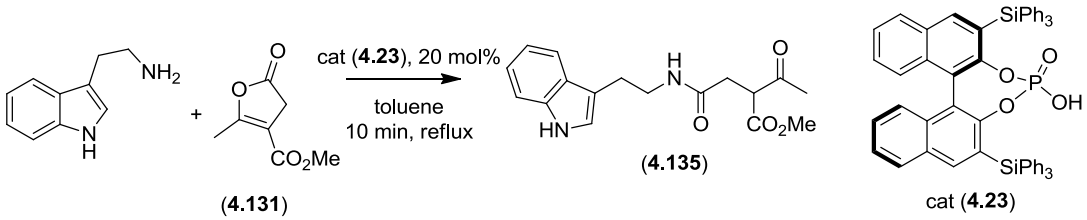
7.4.8.4 Synthesis and characterisation of (1*R*,11b*S*)-10,11b-dimethyl-1-(phenylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.121**)



Following the general procedure the titled compound was obtained after 34 + 72 hours at reflux in the presence of (**4.57**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 3 : 2) (75 mg, 95%). The ee was determined by HPLC using a Chiralpak OD-H column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 14.3 min, major t_R = 17.1 min (72% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.8**).

7.4.9 Evidence for the proposed cyclisation mechanism: initial oxoamide formation

7.4.9.1 Synthesis and characterisation of methyl methyl 2-acetyl-4-{[2-(1*H*-indol-3-yl)ethyl]amino}-4-oxobutanoate (**4.135**)



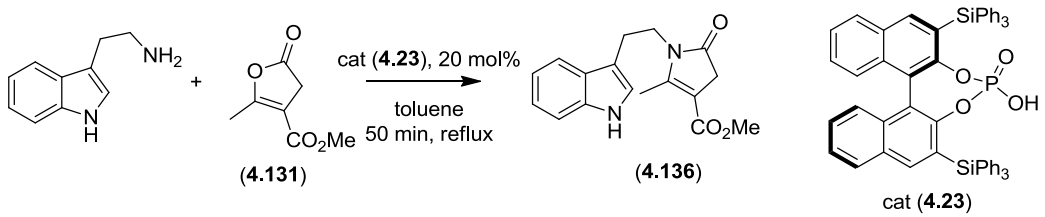
A cyclization reaction between tryptamine and enol lactone (**4.131**) was performed under the conditions aforementioned for doubly substituted lactones, on 0.2 mmol scale, but the reaction was stopped after 10 minutes. The solvent was removed *in vacuo* and the residue immediately purified by column chromatography on silica gel eluting with dichloromethane : acetone, 9 : 1 to afford 41 mg of oxoamide intermediate (**4.135**) (65%) as a colorless oil.

ν_{max}(film)/cm^{-1} 3396 (br w, N-H), 3309 (br w, N-H), 1740 (s, C=O), 1715 (s, C=O), 1653 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.35 (s, 3H, C(O)C$\underline{H}_3$), 2.61 (dd, 1H, *J* = 16.0 Hz, *J* = 6.5 Hz, C$\underline{H}_A$H$_B$CHCO$_2$CH$_3$), 2.73 (dd, 1H, *J* = 16.0 Hz, *J* = 8.0 Hz, CH$_A\underline{H}_B$CHCO$_2$CH$_3$), 2.93 (t, 2H, *J* = 7.0 Hz, NHCH$_2$C$\underline{H}_2$C), 3.54 (m, 2H, NHC$\underline{H}_2$CH$_2$C), 3.72 (s, 3H, OC$\underline{H}_3$), 4.12 (dd, 1H, *J* = 8.0 Hz, *J* = 6.5 Hz, CH$_2$C$\underline{H}$CO$_2$CH$_3$), 5.77 (br t, 1H, *J* = 5.0 Hz, N$\underline{H}$CH$_2$), 7.01 (d, 1H, *J* = 1.5 Hz, NHC$\underline{H}$), 7.12 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.20 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.37 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.58 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.33 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 25.2 (NHCH$_2\underline{C}$H$_2$C), 30.2 (C(O)$\underline{C}$H$_3$), 34.2 ($\underline{C}$H$_2$CHCO$_2$CH$_3$), 39.8 (NH$\underline{C}$H$_2$CH$_2$C), 52.7 (O$\underline{C}$H$_3$), 54.5 (CH$_2\underline{C}$HCO$_2$CH$_3$), 111.3

(ArC-H), 112.6 (ArC-quat), 118.6 (ArC-H), 119.4 (ArC-H), 122.1 (ArC-H), 122.3 (NHCH), 127.2 (ArC-quat), 136.4 (ArC-quat), 169.4 (CO), 169.9 (CO), 202.7 (CO); ***m/z* (ES$^+$)** 339 ([M+Na]$^+$, 60%), 655 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 339.1316 for $C_{17}H_{20}N_2O_4Na^+$ [M+Na]$^+$, requires 339.1315

7.4.10 Evidence for the proposed DYKAT mechanism: pro-chiral enamide

7.4.10.1 Synthesis and characterisation of methyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**4.136**)



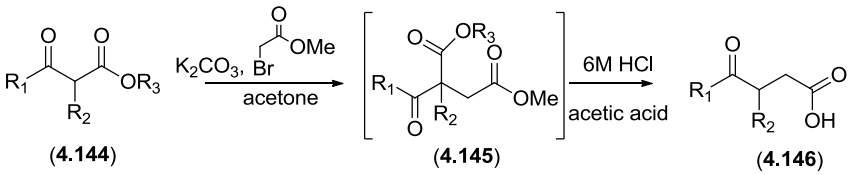
(**4.131**) (**4.136**) cat (**4.23**)

A cyclization reaction between tryptamine and enol lactone (**4.131**) was performed under the conditions previously mentioned for doubly substituted lactones, on 0.2 mmol scale, but the reaction was stopped after 50 minutes and quenched with triethylamine (150 µL for 0.2 mmol scale reaction). The solvent was removed *in vacuo* and the residue immediately purified by column chromatography on deactivated silica gel (1% triethylamine in the eluent), eluting with petroleum ether : ethyl acetate : triethylamine, 60 : 40 : 1 to afford 26 mg of enamide intermediate (**4.136**) (43%) as a colorless solid.

M.P. 158-160 ^oC; **ν_{max}(film)/cm^{-1}** 3337 (br w, N-H), 1688 (s, C=O), 1628 (s, C=C); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 2.16 (t, 3H, *J* = 2.5 Hz, CH_3C), 2.90 (t, 2H, *J* = 7.5 Hz, NCH_2CH_2C), 3.22 (q, 2H, *J* = 2.5 Hz, $C(O)CH_2C$), 3.61 (s, 3H, OCH_3), 3.70 (t, 2H, *J* = 7.5 Hz, NCH_2CH_2C), 6.99 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.07 (td, 1H, *J* = 7.5 Hz, *J* = 1.0 Hz, Ar-H), 7.15 (d, 1H, *J* = 2.0 Hz, NHCH), 7.34 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.54 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.87 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 12.5 (CH_3C), 25.1 (NCH_2CH_2C), 37.8 ($C(O)CH_2C$), 41.5 (NCH_2CH_2C), 51.5 (OCH_3), 102.2 (C-quat), 111.4 (C-quat), 112.3 (ArC-H), 118.9 (ArC-H), 119.3 (ArC-H), 121.9 (ArC-H), 124.1 (NHCH), 127.9 (ArC-quat), 137.0 (ArC-quat), 156.1 (ArC-quat), 165.8 (CO), 176.0 (CO); ***m/z* (ES$^+$)** 357 ([M+MeCN+NH$_4$]$^+$, 100%); **HRMS ES (+)** Found 321.1210 for $C_{17}H_{18}N_2O_3Na^+$ [M+Na]$^+$, requires 321.1210.

In boiling toluene, in the presence of a catalytic amount of *para*-toluenesulfonic acid, the enamide readily cyclized to form a single diastereomer of (±)-(**4.116**).

7.4.11 Preparation of 4-oxo carboxylic acids (**4.146**)



(**4.144**) (**4.145**) (**4.146**)

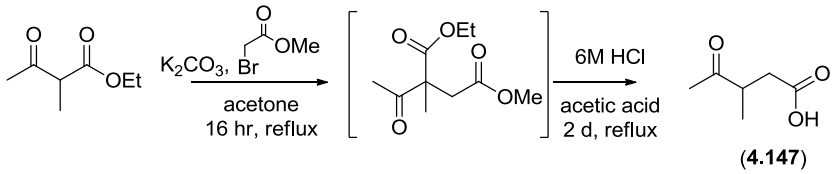
Entry	Compound no.	R_1	R_2	R_3	Yield of (**4.146**)
1	(**4.147**)	Me	Me	Et	37%
2	(**4.148**)	Me	Et	Me	52%
3	(**4.149**)	Me	Bu	Et	47%
4	(**4.150**)	Me	Bn	Et	23%
5	(**4.151**)	$-CH_2CH_2-$	$-CH_2-$	Et	49%
6	(**4.152**)	$-CH_2CH_2CH_2-$	$-CH_2CH_2-$	Me	57%

General procedure for the preparation of 4-oxo carboxylic acids

To a solution of ketone (**4.144**) (1 equivalent) in acetone (3 mL per 1 mmol of ketone) was added anhydrous potassium carbonate (5 equivalents) followed by methyl 2-bromoacetate (1 equivalent). The heterogeneous mixture was heated to reflux for 16 hours. It was allowed to cool to room temperature and water was added (volume identical to acetone). The solution was extracted with diethyl ether (3 x volume of water added). The combined organic layers were concentrated *in vacuo* to afford the crude 2-alkylsuccinate.

The crude 2-alkylsuccinate mixture was dissolved in 6 M HCl aq. (3 mL per 1 g of mixture) and acetic acid (3 mL per 1 g of mixture). The biphasic mixture was heated to reflux for 2 days. It was allowed to cool to room temperature and water was added (volume identical to the combined volume of 6 M HCl aq. and acetic acid). The solution was extracted with CH_2Cl_2 (3 x volume of water added). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the crude 4-oxo carboxylate. The residue was purified by chromatography on silica gel to afford the title compound.

7.4.11.1 Synthesis and characterisation of (±)-3-methyl-4-oxopentanoic acid (**4.147**)[89]

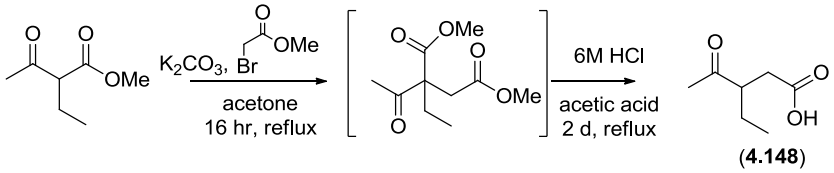


(**4.147**)

Synthesised on a 2.00 g scale (17 mmol) of ethyl 2-methyl-3-oxobutanoatete. The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 648 mg of colorless oil (37% over 2 steps).

ν_{max}(film)/cm^{-1} 3350 (br w, O-H), 1713 (br m, C=O), 1279 (m, C-O), 1171 (m, C-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.19 (d, 3H, *J* = 8.0 Hz, $C\underline{H}_3CH$), 2.22 (s, 3H, $C\underline{H}_3C(O)$), 2.34 (dd, 1H, *J* = 17.1 Hz, *J* = 5.2 Hz, $CHC\underline{H}_A\underline{H}_B$), 2.81 (dd, 1H, *J* = 17.1 Hz, *J* = 8.7 Hz, $CHCH_A\underline{H}_B$), 2.94-3.05 (m, 1H, $CH_3C\underline{H}$), 9.30 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 16.5 ($\underline{C}H_3CH$), 28.3 ($\underline{C}H_3C(O)$), 36.5 ($CH\underline{C}H_2$), 42.5 ($\underline{C}HCH_2$), 178.1 (CO), 210.7 (CO); ***m/z* (ES$^+$)** 129 ([M-H]$^-$, 50%).

7.4.11.2 Synthesis and characterisation of (±)-3-ethyl-4-oxopentanoic acid (**4.148**)

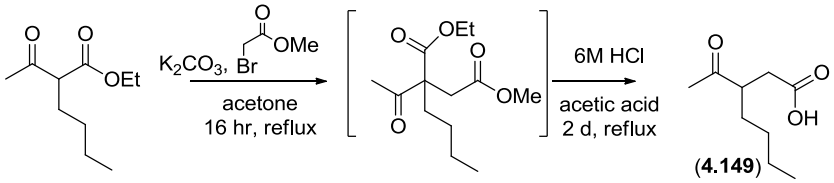


(**4.148**)

Synthesised on 3.00 g scale of methyl 2-ethyl-3-oxobutanoate (20 mmol). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 1.49 g of colorless oil (52% over 2 steps).

ν_{max}(film)/cm^{-1} 3150 (br s, O-H), 1712 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.91 (t, 3H, *J* = 7.4 Hz, $C\underline{H}_3CH_2$), 1.45-1.58 (m, 1H, $CH_3C\underline{H}_A\underline{H}_B$), 1.63-1.75 (m, 1H, $CH_3CH_A\underline{H}_B$), 2.22 (s, 3H, $C\underline{H}_3C(O)$), 2.38 (dd, 1H, *J* = 17.1 Hz, *J* = 4.2 Hz, $CHC\underline{H}_A\underline{H}_B$), 2.79 (dd, 1H, *J* = 17.1 Hz, *J* = 9.8 Hz, $CHCH_A\underline{H}_B$), 2.88-2.97 (m, 1H, $C\underline{H}CH_2$), 10.17 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 11.1 ($\underline{C}H_3CH_2$), 24.2 ($CH_3\underline{C}H_2$), 29.4 ($\underline{C}H_3(CO)$), 34.3 ($CH\underline{C}H_2$), 48.9 ($\underline{C}HCH_2$), 178.5 (CO), 210.8 (CO); ***m/z* (ES$^-$)** 143 ([M-H]$^-$, 40%), 309 ([2(M-H)+Na]$^-$, 100%), **HRMS ES (+)** Found 167.0686 for $C_7H_{12}O_3Na^+$ [M+Na]$^+$, requires 167.0679.

7.4.11.3 Synthesis and characterisation of (±)-3-acetylheptanoic acid (**4.149**)



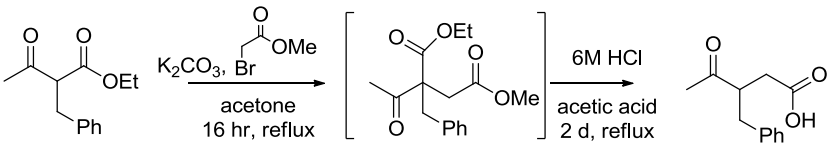
(**4.149**)

Synthesised on 2.00 g scale of ethyl 2-acetylhexanoate (11 mmol). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 865 mg of colorless oil (47% over 2 steps).

ν_{max}(film)/cm^{-1} 2200 (br w, O-H), 1712 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.86 (t, 3H, *J* = 6.9 Hz, $C\underline{H}_3CH_2$), 1.17-1.33 (m, 4H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$), 1.34-1.45 (m, 1H, $CHC\underline{H}_A\underline{H}_BCH_2$),

1.54-1.64 (m, 1H, $CHCH_A\underline{H}_BCH_2$), 2.19 (s, 3H, $C\underline{H}_3C(O)$), 2.36 (dd, 1H, *J* = 17.2 Hz, *J* = 4.2 Hz, $CHC\underline{H}_AH_BCO_2H$), 2.76 (dd, 1H, *J* = 17.2 Hz, *J* = 9.9 Hz, $CHCH_A\underline{H}_BCO_2H$), 2.89-2.87 (m, 1H, $C\underline{H}CH_2$), 11.14 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 13.8 ($\underline{C}H_3CH_2$), 22.6 & 28.9 ($CH_3\underline{C}H_2$, $CH_3CH_2\underline{C}H_2$), 29.4 ($\underline{C}H_3C(O)$), 30.8 ($CH\underline{C}H_2CH_2$) 34.8 ($CH\underline{C}H_2CO_2H$), 47.6 ($\underline{C}HCH_2$), 178.5 (CO), 210.8 (CO); ***m/z* (ES$^+$)** 195 ($[M+Na]^+$, 55%), 367 ($[2M+Na]^+$, 100%); **HRMS ES (+)** Found 195.0997 for $C_9H_{16}O_3Na^+$ $[M+Na]^+$, requires 195.0992.

7.4.11.4 Synthesis and characterisation of (±)-3-benzyl-4-oxopentanoic acid (**4.150**)[90]

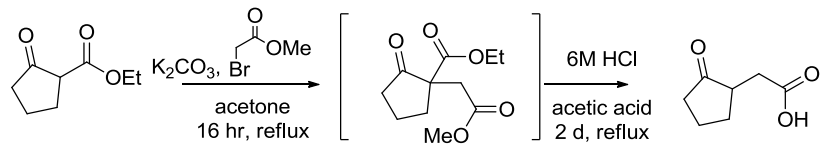


(**4.150**)

Synthesized on 5.00 g scale of ethyl 2-benzylacetoacetate (23 mmol). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 1.08 g of colourless solid (23% over 2 steps).

M.P. 85-87 ºC; **ν_{max}(film)/cm^{-1}** 3087 (br w, O-H), 1710 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 2.11 (s, 3H, $C(O)C\underline{H}_3$), 2.37 (dd, 1H, *J* = 17.6 Hz, *J* = 3.8 Hz, $C\underline{H}_AH_BCO_2H$), 2.61 (dd, 1H, *J* = 13.6 Hz, *J* = 8.3 Hz, $CHCC\underline{H}_AH_BCH$), 2.80 (dd, 1H, *J* = 17.6 Hz, *J* = 10.1 Hz, $CH_A\underline{H}_BCO_2H$), 2.94 (dd, 1H, *J* = 13.6 Hz, *J* = 6.9 Hz, $CHCCH_A\underline{H}_BCH$), 3.20-3.29 (m, 1H, $C(O)C\underline{H}$), 7.16 (d, 2H, *J* = 7.6 Hz, 2 x Ar-H), 7.21-7.27 (m, 1H, Ar-H), 7.31 (t, 2H, *J* = 7.6 Hz, 2 x Ar-H), 10.32 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 30.2 ($C(O)\underline{C}H_3$), 34.9 ($\underline{C}H_2CO_2H$), 37.6 ($CHC\underline{C}H_2CH$), 49.5 ($C(O)\underline{C}H$), 126.9 (Ar$\underline{C}$-H), 128.8 (2 x Ar$\underline{C}$-H), 128.9 (2 x Ar$\underline{C}$-H), 138.0 ($CH\underline{C}CH_2$), 178.2 (CO), 210.8 (CO); ***m/z* (ES$^-$)** 205 ($[M-H]^-$, 75%); **HRMS ES (+)** Found 229.0833 for $C_{12}H_{14}O_3Na^+$ $[M+Na]^+$, requires 229.0835.

7.4.11.5 Synthesis and characterisation of (±)-(2-oxocyclopentyl)acetic acid (**4.151**)[91]

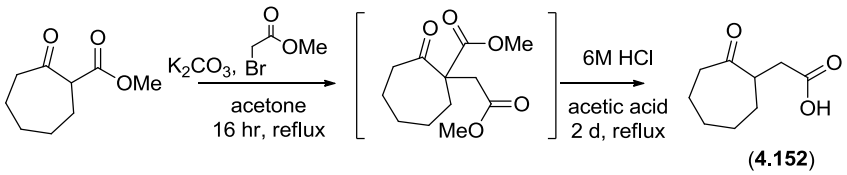


(**4.151**)

Synthesised on 3.00 g scale of ethyl 2-oxocyclopentanecarboxylate (19 mmol). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 1.06 g of colorless crystalline solid (49% over 2 steps).

M.P. 43-45 °C (lit. 50-53 °C); **ν_{max}(film)/cm^{-1}** 3250 (br m, OH), 1734 (br s, C=O), 1273 (s, C-O), 1163 (s, C-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.57-1.70 (m, 1H, C$\underline{H}_A$H$_B$), 1.75-1.89 (m, 1H, CH$_A\underline{H}_B$), 2.02-2.23 (m, 2H, C$\underline{H}_2$) , 2.29-2.51 (m, 4H, C$\underline{H}_2$, CHC$\underline{H}_A$H$_B$CO$_2$H, C$\underline{H}$CH$_2$), 2.74-2.83 (m, 1H, CHCH$_A\underline{H}_B$CO$_2$H), 10.67 (br s, 1H, OH); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.6 (C$\underline{H}_2$), 29.2 (C$\underline{H}_2$), 33.7 (CH$\underline{C}$H$_2$CO$_2$H), 37.4 (C$\underline{H}_2$), 45.4 (C$\underline{H}$CH$_2$), 178.1 (CO), 219.3 (CO); ***m/z* (ES$^+$)** 165 ([M+Na]$^+$, 80%); **HRMS ES (+)** Found 165.0521 for $C_7H_{10}O_3Na^+$ [M+Na]$^+$, requires 165.0522.

7.4.11.6 Synthesis and characterisation of (±)-(2-oxocycloheptyl)acetic acid (**4.152**)

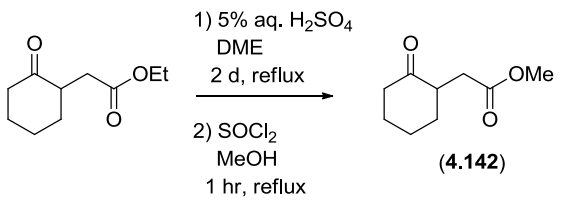


(**4.152**)

Synthesised on 3.00 g scale of methyl 2-oxocycloheptanecarboxylate (19 mmol). The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 1.87 g of colorless oil (57% over 2 steps).

ν_{max}(film)/cm^{-1} 3095 (br s, O-H), 1699 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.23-1.44 (m, 2H, C$\underline{H}_2$), 1.50-1.62 (m, 1H, C$\underline{H}_A$H$_B$), 1.68-1.96 (m, 5H, 2 x C$\underline{H}_2$, CH$_A\underline{H}_B$), 2.34 (dd, 1H, *J* = 17.0 Hz, *J* = 6.6 Hz, CHC$\underline{H}_A$H$_B$CO$_2$H), 2.40-2.50 (m, 1H, C(O)C$\underline{H}_A$H$_B$CH$_2$), 2.63 (dt, 1H, *J* = 8.9 Hz, *J* = 4.2 Hz, C(O)CH$_A\underline{H}_B$CH$_2$), 2.85 (dd, 1H, *J* = 17.1 Hz, *J* = 8.4 Hz, CHCH$_A\underline{H}_B$CO$_2$H), 3.04-3.12 (m, 1H, C$\underline{H}$CH$_2$), 10.33 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 23.4 & 28.9 & 29.3 & 31.1 (4 x C$\underline{H}_2$), 36.4 (CH$\underline{C}$H$_2$CO$_2$H), 43.3 (C(O)$\underline{C}$H$_2$CH$_2$), 47.2 (C$\underline{H}$CH2), 178.4 (CO), 214.3 (CO); ***m/z* (ES$^-$)** 169 ([M-H]$^-$, 60%), 361 ([2(M-H)+Na]$^-$, 100%); **HRMS ES (+)** Found 215.0655 for $C_9H_{13}O_3Na_2^+$ [M-H+2Na]$^+$, requires 215.0655.

7.4.11.7 Synthesis and characterisation of (±)-methyl (2-oxocyclohexyl)acetate (**4.142**)



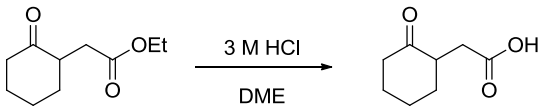
(**4.142**)

To a solution of ethyl 2-(2-oxocyclohexyl)acetate (2.00 mL, 11 mmol) in DME (30 mL) was added 5% aqueous H_2SO_4 solution (30 mL) and the solution was heated to reflux for 2 days before quenching with water (30 mL) and extracting with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the crude oxoacid. It

was dissolved in methanol (20 mL) and cooled to 0 ºC before adding thionyl chloride (12 mmol, 1.43 g, 0.88 mL) dropwise. The solution was heated to reflux for 1 hour before cooling, evaporating the solution *in vacuo* and adding a saturated solution of $NaHCO_3$ (20 mL). The solution was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the crude oxoester. The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 1.58 g of colorless oil (84%).

ν_{max}(film)/cm^{-1} 1739 (s, C=O), 1712 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.34-1.47 (m, 1H, $CHC\underline{H}_A H_B CH_2$), 1.56-1.79 (m, 2H, $C(O)CH_2C\underline{H}_A H_B$, $C(O)CH_2CH_2C\underline{H}_A H_B$), 1.84-1.92 (m, 1H, $C(O)CH_2CH_2CH_A\underline{H}_B$), 2.06-2.18 (m, 3H, $CHC\underline{H}_A H_B CO_2H$, $C(O)CH_2CH_A\underline{H}_B$, $CHCH_A\underline{H}_B CH_2$), 2.31-2.45 (m, 2H, $C(O)C\underline{H}_2CH_2$), 2.73-2.81 (m, 1H, $CHCH_A\underline{H}_B CO_2H$), 2.81-2.91 (m, 1H, $C\underline{H}CH_2$), 3.66 (s, 3H, $C\underline{H}_3O$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 25.2 ($CHCH_2\underline{C}H_2$), 27.8 ($C(O)CH_2\underline{C}H_2$), 33.9 ($CH\underline{C}H_2CH_2$), 34.0 ($CH\underline{C}H_2CO_2H$), 41.8 ($C(O)\underline{C}H_2CH_2$), 47.0 ($\underline{C}HCH_2$), 51.7 ($\underline{C}H_3O$), 173.1 (CO), 211.1 (CO); ***m/z* (ES$^+$)** 193 ($[M+Na]^+$, 50%), 363 ($[2M+Na]^+$, 100%); **HRMS ES (+)** Found 193.0842 for $C_9H_{14}O_3Na^+$ $[M+Na]^+$, requires 193.0835.

7.4.11.8 Synthesis and characterisation of (±)-(2-oxocyclohexyl)acetic acid (**4.143**)

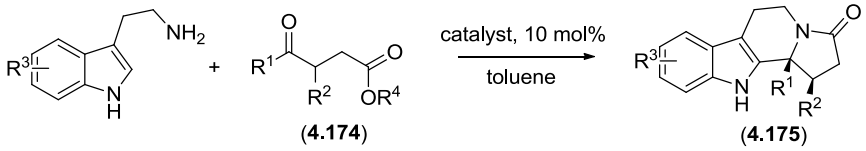


(**4.143**)

To a solution of ethyl 2-(2-oxocyclohexyl)acetate (1.96 mL, 10.8 mmol) in DME (10 mL) was added 3 M aqueous HCl (10 mL) and the solution was heated to reflux for 2 days. It was allowed to cool to room temperature and a saturated solution of Na_2CO_3 (20 mL) was added. The solution was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with a saturated solution of Na_2CO_3 (2 x 20 mL). The combined aqueous layers were acidified to pH 1 with 6 M aqueous HCl and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the crude oxoacid. The product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 9 : 1 to give 431 mg of colorless oil (26%).

ν_{max}(film)/cm^{-1} 3095 (br m, O-H), 1709 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.36-1.49 (m, 1H, $CHC\underline{H}_A H_B CH_2$), 1.57-1.79 (m, 2H, $C(O)CH_2C\underline{H}_A H_B CH_2$, $CHCH_2C\underline{H}_A H_B$), 1.85-1.93 (m, 1H, $CHCH_2CH_A\underline{H}_B$), 2.07-2.25 (m, 3H, $CHC\underline{H}_A H_B CO_2H$, $CHCH_A\underline{H}_B CH_2$, $C(O)CH_2CH_A\underline{H}_B CH_2$), 2.31-2.48 (m, 2H, $C(O)C\underline{H}_2CH_2$), 2.77-2.89 (m, 2H, $C\underline{H}CH_2$, $CHCH_A\underline{H}_B CO_2H$), 10.01 (br s, 1H, O-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 25.1 ($CHCH_2\underline{C}H_2$), 27.7 ($C(O)CH_2\underline{C}H_2$), 33.8 ($CH\underline{C}H_2CH_2$), 34.3 ($CH\underline{C}H_2CO_2H$), 41.8 ($C(O)\underline{C}H_2CH_2$), 46.9 ($\underline{C}HCH_2$), 178.5 (CO), 211.1 (CO); ***m/z* (ES$^-$)** 155 ($[M-H]^-$, 90%); **HRMS ES (+)** Found 179.0679 for $C_8H_{12}O_3Na^+$ $[M+Na]^+$, requires 179.0679.

7.4.12 Preparation of cyclised β-carbolines (**4.175**)

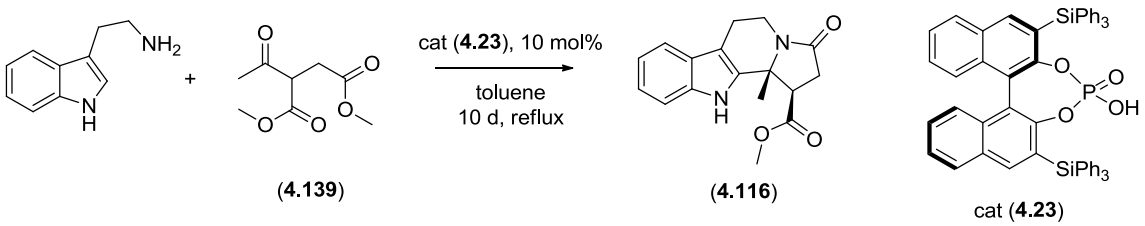


General procedure for the preparation of cyclized β-carbolines (**4.175**)

4-oxo carboxylate (**4.174**) (0.2 mmol, 1 equivalent) was dissolved in toluene (42 mL) and a tryptamine derivative (0.2 mmol, 1 equivalent) was added in one portion at room temperature, immediately followed by the addition of a phosphoric acid catalyst (0.02 mmol, 0.1 equivalents) in one portion. The resulting suspension was heated under reflux until complete consumption of starters (TLC monitoring). The solvent was removed *in vacuo*, and the residue purified by chromatography on silica gel (see below for eluent systems).

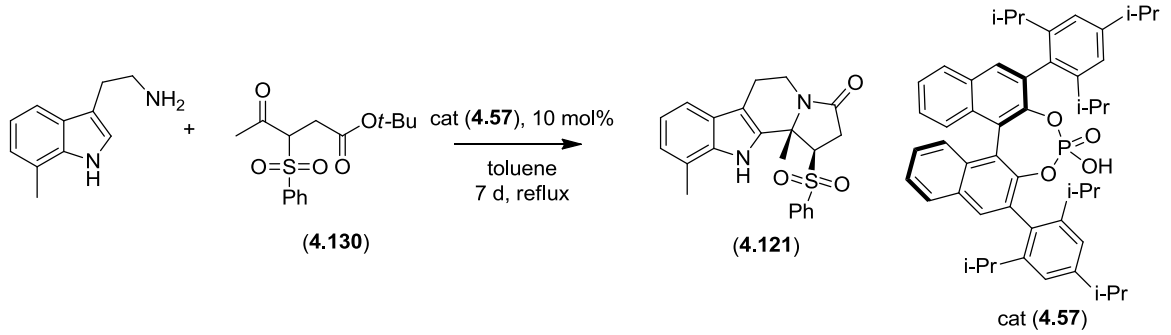
Note: All racemates were prepared using *para*-toluenesulfonic acid (0.1 equivalents) in refluxing toluene, in conditions similar to the enantioselective cascade (identical concentration, same reagents purity *etc.*).

7.4.12.1 Synthesis and characterisation of methyl (1*R*,11b*R*)-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-1-carboxylate (**4.116**)



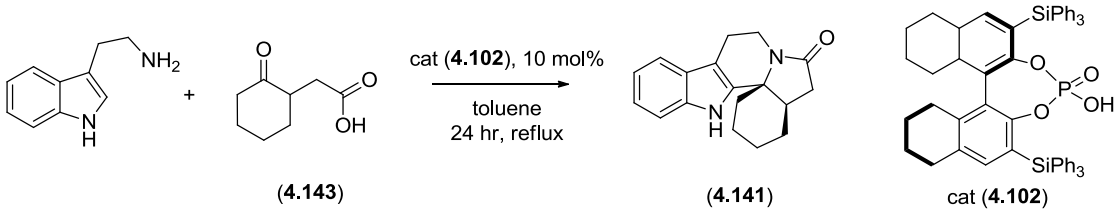
Following the general procedure the titled compound was obtained as a single diastereomer after 10 days at reflux in the presence of (**4.23**) as a colourless crystalline solid following flash silica gel chromatography (increasing polarity from ethyl acetate : petroleum ether, 1 : 1 to ethyl acetate) (47 mg, 78%). The ee was determined by HPLC using a Chiralpak IB column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 12.6 min, minor t_R = 20.1 min (69% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.3**).

7.4.12.2 Synthesis and characterisation of (1*R*,11b*S*)-10,11b-dimethyl-1-(phenylsulfonyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.121**)



Following the general procedure the titled compound was obtained as a single diastereomer after 7 days at reflux in the presence of (**4.57**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 3 : 2) (64 mg, 81%). The ee was determined by HPLC using a Chiralpak OD-H column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 14.7 min, major t_R = 17.4 min (68% ee). The spectroscopic data of the titled product was identical to that previously described (**7.4.5.8**). $\mathbf{[\alpha]_D^{21}}$ = + 222.3 (c = 0.528 in $CHCl_3$).

7.4.12.3 Synthesis and characterisation of (4a*R*,14b*R*)-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (**4.141**)

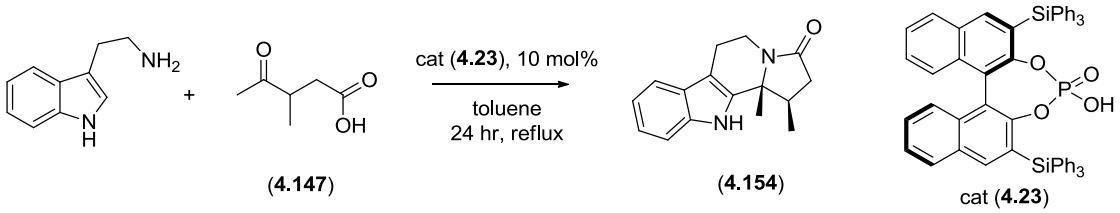


Following the general procedure the reaction was carried out on a 0.1 mmol scale. The titled compound was obtained after 24 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate) (18 mg, 63%). The ee was determined by HPLC using a Chiralpak AD column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 5.7 min, minor t_R = 10.7 min (68% ee), >98:2 dr.

M.P. 241-244 ^oC; $\mathbf{[\alpha]_D^{25}}$ = + 116.1 (c = 1.0 in $CHCl_3$); $\mathbf{\nu_{max}(film)/cm^{-1}}$ 3305 (br w, N-H), 1666 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.55-1.68 (m, 2H, C$\underline{H}_2$), 1.73-1.85 (m, 3H, NCC$\underline{H}_A$H$_B$CH$_2$, C$\underline{H}_2$), 1.87-2.04 (m, 2H, CHC$\underline{H}_2$CH$_2$), 2.19-2.26 (m, 1H, NCCH$_A\underline{H}_B$CH$_2$), 2.37-2.45 (m, 1H, C(O)C$\underline{H}_A$H$_B$CH), 2.48-2.59 (m, 2H, C(O)CH$_A\underline{H}_B$CH, C(O)CH$_2$C$\underline{H}$), 2.78-2.94 (m, 2H, NCH$_2$C$\underline{H}_2$), 3.09-3.17 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$), 4.46 (dd, 1H, *J* = 13.2 Hz, *J* = 5.4 Hz, NCH$_A\underline{H}_B$CH$_2$), 7.14 (t, 1H, *J*

= 7.1 Hz, Ar-H), 7.21 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.39 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.36 (br s, 1H, N-H); **^{13}C NMR: δ_C** ($CDCl_3$, 100 MHz) 20.3 & 21.1 ($NCCH_2\underline{C}H_2$, $CHCH_2\underline{C}H_2$), 22.0 ($NCH_2\underline{C}H_2$), 26.2 ($CH\underline{C}H_2CH_2$), 34.2 ($NC\underline{C}H_2CH_2$), 34.7 ($N\underline{C}H_2CH_2$), 35.6 ($C(O)C\underline{H}_2CH$), 38.0 ($\underline{C}HCH_2$), 60.2 ($CH_2\underline{C}N$), 107.1 (Ar<u>C</u>-quat), 111.1 (Ar<u>C</u>-H), 118.5 (Ar<u>C</u>-H), 119.9 (Ar<u>C</u>-H), 122.2 (Ar<u>C</u>-H), 126.5 (Ar<u>C</u>-quat), 135.9 (Ar<u>C</u>-quat), 138.0 (Ar<u>C</u>-quat), 172.0 (CO); ***m/z* (ES$^-$)** 279 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 303.1467 for $C_{18}H_{20}N_2ONa^+$ $[M+Na]^+$, requires 303.1468.

7.4.12.4 Synthesis and characterisation of (1*R*,11b*R*)-1,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.154**)

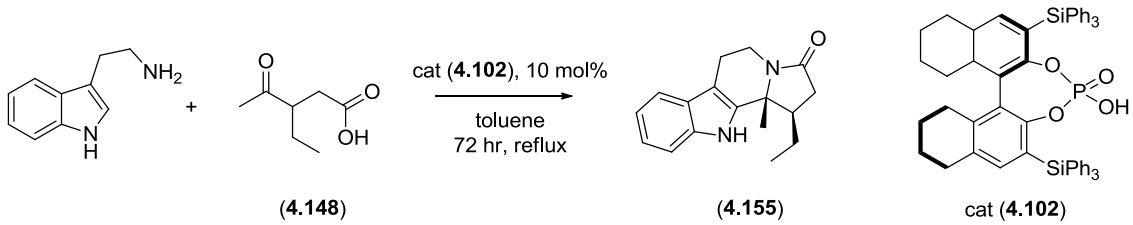


(**4.147**) (**4.154**) cat (**4.23**)

Following the general procedure the titled compound was obtained after 24 hours at reflux in the presence of (**4.23**) as a colourless oil following flash silica gel chromatography (ethyl acetate) (54 mg, 99%). The ee was determined by HPLC using a Chiralpak OD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 25.3 min, major t_R = 30.9 min (76% ee), dr = 97:3.

$[\alpha]_D^{25}$ = + 66.6 (c = 0.94 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3271 (br w, N-H), 1664 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.42 (d, 3H, *J* = 6.6 Hz, $C\underline{H}_3CH$), 1.51 (s, 3H, $C\underline{H}_3C$), 2.34-2.41 (m, 1H, $C(O)C\underline{H}_AH_BCH$), 2.50-2.62 (m, 2H, $C(O)CH_A\underline{H}_BCH$, $C(O)CH_2C\underline{H}$), 2.85-2.89 (m, 2H, $NCH_2C\underline{H}_2$), 3.05-3.12 (m, 1H, $NC\underline{H}_AH_BCH_2$), 4.53-4.58 (m, 1H, $NCH_A\underline{H}_BCH_2$), 7.17-7.21 (m, 1H, Ar-H), 7.24-7.28 (m, 1H, Ar-H), 7.41 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.55 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.01 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.8 ($\underline{C}H_3CH$), 19.3 ($\underline{C}H_3$), 21.5 ($NCH_2\underline{C}H_2$), 35.0 ($N\underline{C}H_2CH_2$), 38.8 ($C(O)\underline{C}H_2CH$), 39.2 ($\underline{C}HCH_2$), 61.6 ($CH_3\underline{C}$), 107.1 (Ar<u>C</u>-quat), 111.0 (Ar<u>C</u>-H), 118.5 (Ar<u>C</u>-H), 119.9 (Ar<u>C</u>-H), 122.2 (Ar<u>C</u>-H), 126.6 (Ar<u>C</u>-quat), 136.1 (Ar<u>C</u>-quat), 137.9 (Ar<u>C</u>-quat), 171.9 (CO); ***m/z* (ES$^-$)** 253 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 277.1312 for $C_{16}H_{18}N_2ONa^+$ $[M+Na]^+$, requires 277.1311.

7.4.12.5 Synthesis and characterisation of (1*R*,11b*R*)-1-ethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.155**)

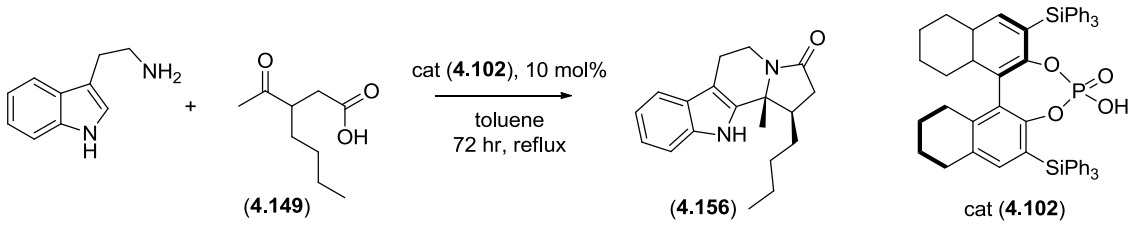


(**4.148**) (**4.155**) cat (**4.102**)

Following the general procedure the titled compound was obtained after 72 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (dichloromethane : acetone, 9 : 1) (18 mg, 34%). The ee was determined by HPLC using a Chiralpak AD column (95:5 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 24.7 min, minor t_R = 36.6 min (61% ee), >98:2 dr.

M.P. 110-115 **º**C; **$[\alpha]_D^{25}$** = + 58.0 (c = 2.0 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3276 (br w, N-H), 1668 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.04 (t, 3H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.47 (s, 3H, $CC\underline{H}_3$), 1.59-1.72 (m, 1H, $C\underline{H}_AH_BCH_3$), 1.87-2.00 (m, 1H, $CH_A\underline{H}_BCH_3$), 2.23-2.35 (m, 2H, $C(O)CH_2C\underline{H}$, $C(O)C\underline{H}_AH_BCH$), 2.57-2.69 (m, 1H, $C(O)CH_A\underline{H}_BCH$), 2.80-2.85 (m, 2H, $NCH_2C\underline{H}_2$), 3.00-3.09 (m, 1H, $NC\underline{H}_AH_BCH_2$), 4.47-4.54 (m, 1H, $NCH_A\underline{H}_BCH_2$), 7.14 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.21 (t, 1H, *J* = 7.1 Hz, Ar-H), 7.37 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.18 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 12.8 ($CH_2\underline{C}H_3$), 19.8 ($C\underline{C}H_3$), 21.5 ($\underline{C}H_2$), 23.6 ($\underline{C}H_2$), 34.8 ($N\underline{C}H_2CH_2$), 36.6 ($C(O)\underline{C}H_2CH$), 46.5 ($C(O)CH_2\underline{C}H$), 61.6 ($CH_3\underline{C}$), 107.2 (Ar$\underline{C}$-quat), 111.0 (Ar$\underline{C}$-H), 118.5 (Ar$\underline{C}$-H), 119.9 (Ar$\underline{C}$-H), 122.2 (Ar$\underline{C}$-H), 126.6 (Ar$\underline{C}$-quat), 136.0 (Ar$\underline{C}$-quat), 137.9 (Ar$\underline{C}$-quat), 171.7 (CO); ***m/z* (ES$^-$)** 267 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 291.1470 for $C_{17}H_{20}N_2ONa^+$ $[M+Na]^+$, requires 291.1468.

7.4.12.6 Synthesis and characterisation of (1*R*,11b*R*)-1-butyl-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.156**)

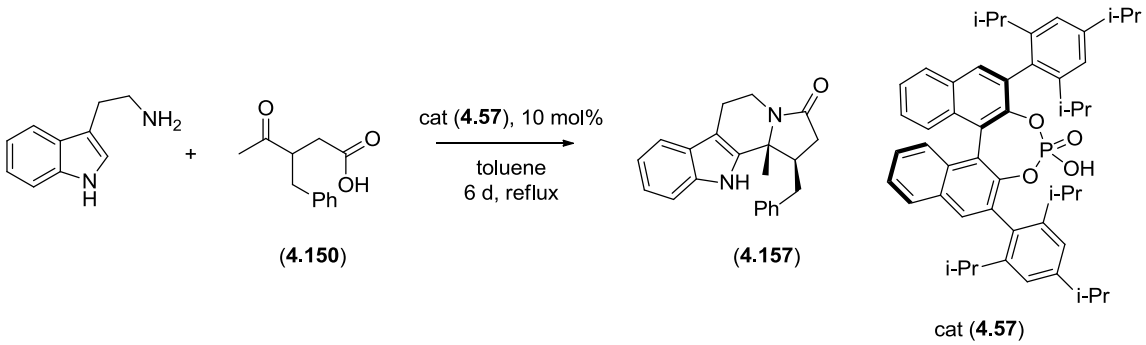


(**4.149**) (**4.156**) cat (**4.102**)

Following the general procedure the reaction was carried out on a 0.1 mmol scale. The titled compound was obtained after 72 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (30 mg, 99%). The ee was determined by HPLC using a Chiralpak OD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 11.3 min, major t_R = 24.5 min (59% ee), dr = 97:3.

M.P. 206-208 ºC; **$[\alpha]_D^{25}$** = + 51.4 (c = 0.74 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3274 (br w, N-H), 1667 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.95 (t, 3H, *J* = 6.6 Hz, $C\underline{H}_3CH_2$), 1.20-1.44 (m, 4H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$), 1.47 (s, 3H, $CC\underline{H}_3$), 1.58-1.70 (m, 1H, $CHC\underline{H}_A\underline{H}_BCH_2$), 1.81-1.95 (m, 1H, $CHCH_A\underline{H}_BCH_2$), 2.24-2.41 (m, 2H, $C(O)CH_2C\underline{H}$, $C(O)C\underline{H}_A\underline{H}_BCH$), 2.61 (dd, 1H, *J* = 14.6 Hz, *J* = 6.5 Hz, $C(O)CH_A\underline{H}_BCH$), 2.80-2.86 (m, 2H, $NCH_2C\underline{H}_2$), 2.99-3.09 (m, 1H, $NC\underline{H}_A\underline{H}_BCH_2$), 4.47-4.54 (m, 1H, $NCH_A\underline{H}_BCH_2$), 7.14 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.21 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.38 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.51 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.26 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 19.8 ($C\underline{C}H_3$), 21.5 ($\underline{C}H_2$), 22.9 ($\underline{C}H_2$), 30.4 ($CH\underline{C}H_2CH_2$), 34.8 ($N\underline{C}H_2CH_2$), 36.9 ($C(O)\underline{C}H_2CH$), 44.7 ($C(O)CH_2\underline{C}H$), 61.6 ($CH_3\underline{C}$), 107.1 (Ar<u>C</u>-quat), 111.0 (Ar<u>C</u>-H), 118.5 (Ar<u>C</u>-H), 119.9 (Ar<u>C</u>-H), 122.2 (Ar<u>C</u>-H), 126.6 (Ar<u>C</u>-quat), 136.1 (Ar<u>C</u>-quat), 138.0 (Ar<u>C</u>-quat), 171.8 (CO); ***m/z* (ES$^-$)** 295 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 319.1782 for $C_{19}H_{24}N_2ONa^+$ $[M+Na]^+$, requires 319.1781.

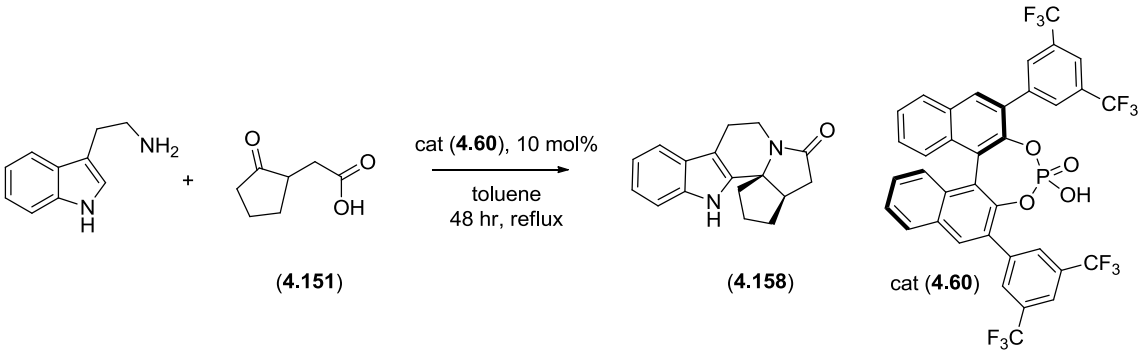
7.4.12.7 Synthesis and characterisation of (1*R*,11b*R*)-1-benzyl-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.157**)



Following the general procedure the titled compound was obtained after 6 days at reflux in the presence of (**4.57**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (30 mg, 46%). The ee was determined by HPLC using a Chiralpak AD column (85:15 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 10.6 min, major t_R = 14.4 min (32% ee), >98:2 dr.

M.P. 100-104 ºC; **$[\alpha]_D^{25}$** = + 25.1 (c = 1.05 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3277 (br w, N-H), 1667 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.57 (s, 3H, $C\underline{H}_3$), 2.47 (dd, 1H, *J* = 16.4 Hz, *J* = 12.3 Hz, $C(O)C\underline{H}_A\underline{H}_BCH_2$), 2.62 (dd, 1H, *J* = 16.4 Hz, *J* = 8.0 Hz, $C(O)CH_A\underline{H}_BCH_2$), 2.75-2.80 (m, 3H, $C(O)CH_2C\underline{H}$, $NCH_2C\underline{H}_2$), 2.96-3.13 (m, 3H, $NC\underline{H}_A\underline{H}_BCH_2$, $CHCC\underline{H}_2$), 4.51 (dt, 1H, *J* = 13.0 Hz, *J* = 3.2 Hz, $NCH_A\underline{H}_BCH_2$), 6.43 (br s, 1H, N-H), 6.91 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.02-7.22 (m, 3H, 3 x Ar-H), 7.32-7.35 (m, 2H, 2 x Ar-H), 7.41-7.49 (m, 3H, 3 x Ar-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.3 ($\underline{C}H_3$), 21.5 ($NCH_2\underline{C}H_2$), 34.9 ($N\underline{C}H_2CH_2$), 36.3 ($CHC\underline{C}H_2$), 37.8 ($C(O)\underline{C}H_2CH$), 46.4 ($C(O)CH_2\underline{C}H$), 62.1 ($CH_3\underline{C}$), 107.2 (Ar<u>C</u>-quat), 110.8 (Ar<u>C</u>-H), 118.3 (Ar<u>C</u>-H), 119.5 (Ar<u>C</u>-H), 122.0 (Ar<u>C</u>-H), 126.1 (Ar<u>C</u>-quat), 127.2 (Ar<u>C</u>-H), 129.4 (2 x Ar<u>C</u>-H), 129.5 (2 x Ar<u>C</u>-H), 135.6 (Ar<u>C</u>-quat), 136.9 (Ar<u>C</u>-quat), 139.6 (Ar<u>C</u>-quat), 171.0 (CO); ***m/z* (ES$^-$)** 329 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 353.1625 for $C_{22}H_{22}N_2ONa^+$ $[M+Na]^+$, requires 353.1624.

7.4.12.8 Synthesis and characterisation of (3a*R*,13b*R*)-2,3,3a,4,8,13-hexahydro-7*H*-cyclopenta[1,8a]indolizino[8,7-*b*]indol-5(1*H*)-one (**4.158**)

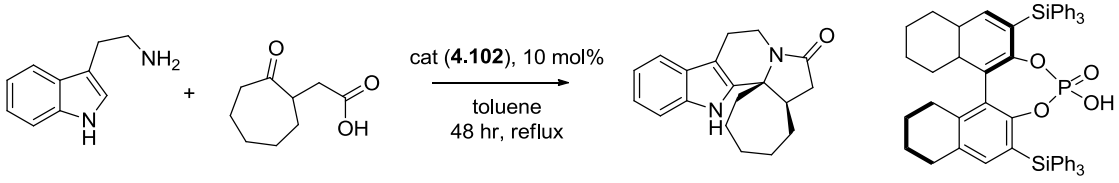


(**4.151**) (**4.158**) cat (**4.60**)

Following the general procedure the titled compound was obtained after 48 hours at reflux in the presence of (**4.60**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 4 : 1) (30 mg, 57%). The ee was determined by HPLC using a Chiralpak AD column (85:15 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 8.9 min, minor t_R = 17.3 min (68% ee), >98:2 dr.

M.P. 80-85 ^{o}C; **$[\alpha]_D^{25}$** = + 31.8 (c = 1.03 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3260 (br w, N-H), 1665 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.75-1.95 (m, 4H, NCC$\underline{H}_2$CH$_2$, NCCH$_2$C$\underline{H}_2$), 2.06-2.22 (m, 2H, CHC$\underline{H}_2$CH$_2$), 2.28 (dd, 1H, *J* = 17.4 Hz, *J* = 4.1 Hz, C(O)C$\underline{H}_A$H$_B$CH), 2.71-2.84 (m, 2H, NCH$_2$C$\underline{H}_A$H$_B$, C(O)CH$_A\underline{H}_B$CH), 2.87-2.96 (m, 2H, NCH$_2$CH$_A\underline{H}_B$, C$\underline{H}$CH$_2$), 3.10 (td, 1H, *J* = 12.1 Hz, *J* = 4.3 Hz, NC$\underline{H}_A$H$_B$CH$_2$), 4.51 (dd, 1H, *J* = 13.1 Hz, *J* = 5.7 Hz, NCH$_A\underline{H}_B$CH$_2$), 7.10-7.14 (m, 1H, Ar-H), 7.16-7.21 (m, 1H, Ar-H), 7.34 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.47 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.21 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.9 (NCH$_2\underline{C}$H$_2$), 24.6 & 35.2 (NC$\underline{C}$H$_2$CH$_2$, NCCH$_2\underline{C}$H$_2$), 36.8 (N$\underline{C}$H$_2$CH$_2$), 39.0 (C(O)$\underline{C}$H$_2$CH), 40.2 (CH$\underline{C}$H$_2$CH$_2$), 41.3 ($\underline{C}$HCH$_2$), 71.0 (CH$_2\underline{C}$N), 108.1 (Ar$\underline{C}$-quat), 111.0 (Ar$\underline{C}$-H), 118.3 (Ar$\underline{C}$-H), 119.8 (Ar$\underline{C}$-H), 122.1 (Ar$\underline{C}$-H), 126.7 (Ar$\underline{C}$-quat), 136.3 (Ar$\underline{C}$-quat), 136.7 (Ar$\underline{C}$-quat), 174.2 (CO); ***m/z* (ES$^-$)** 265 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 289.1312 for $C_{17}H_{18}N_2ONa^+$ [M+Na]$^+$, requires 289.1311.

7.4.12.9 Synthesis and characterisation of (5a*R*,15b*R*)-2,3,4,5,5a,6,10,15-octahydro-9*H*-cyclohepta[1,8a]indolizino[8,7-*b*]indol-7(1*H*)-one (**4.159**)

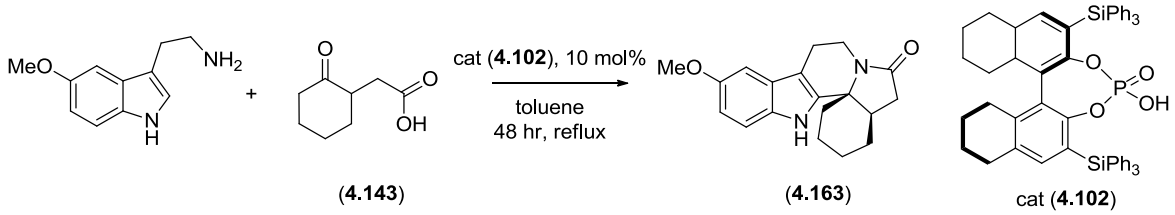


(**4.152**) (**4.159**) cat (**4.102**)

Following the general procedure the titled compound was obtained after 48 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (53 mg, 90%). The ee was determined by HPLC using a Chiralpak AD column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 4.6 min, minor t_R = 9.7 min (86% ee), >98:2 dr.

M.P. 244-247 °C; **$[\alpha]_D^{25}$** = + 58.2 (c = 0.86 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3264 (br w, N-H), 1662 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, D_6-DMSO) 1.21-1.47 (m, 2H, $NCCH_2C\underline{H}_AH_B$, $CHCH_2C\underline{H}_AH_B$), 1.55-1.81 (m, 5H, $NCCH_2CH_A\underline{H}_B$, $CHC\underline{H}_AH_BCH_2$, $CHCH_2CH_2C\underline{H}_2$, $CHCH_2CH_A\underline{H}_B$), 1.95-2.13 (m, 2H, $NCC\underline{H}_2CH_2$), 2.14-2.32 (m, 2H, $C(O)C\underline{H}_AH_BCH$, $CHCH_A\underline{H}_BCH_2$), 2.44-2.52 (m, 1H, $C(O)CH_A\underline{H}_BCH$), 2.56-2.66 (m, 2H, $NCH_2C\underline{H}_2$), 2.67-2.77 (m, 1H, $C\underline{H}CH_2$), 2.97-3.07 (m, 1H, $NC\underline{H}_AH_BCH_2$), 4.22 (dd, 1H, *J* = 13.0 Hz, *J* = 4.7 Hz, $NCH_A\underline{H}_BCH_2$), 6.96 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.05 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.32-7.36 (m, 2H, 2 x Ar-H), 10.90 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, D_6-DMSO) 21.3 ($NCH_2\underline{C}H_2$), 23.8 ($NCCH_2\underline{C}H_2$), 25.1 ($NCCH_2CH_2\underline{C}H_2$), 29.1 ($CH\underline{C}H_2CH_2$), 31.3 ($CHCH_2\underline{C}H_2$), 35.4 & 35.5 ($N\underline{C}H_2CH_2$, $C(O)\underline{C}H_2CH$), 38.3 ($NC\underline{C}H_2CH_2$), 41.6 ($\underline{C}HCH_2$), 66.6 ($CH_2\underline{C}N$), 105.3 (Ar<u>C</u>-quat), 112.1 (Ar<u>C</u>-H), 118.7 (Ar<u>C</u>-H), 119.4 (Ar<u>C</u>-H), 121.8 (Ar<u>C</u>-H), 127.1 (Ar<u>C</u>-quat), 136.9 (Ar<u>C</u>-quat), 141.4 (Ar<u>C</u>-quat), 173.8 (CO); ***m/z* (ES$^-$)** 293 ([M-H]$^-$, 80%); **HRMS ES (+)** Found 317.1624 for $C_{19}H_{22}N_2ONa^+$ $[M+Na]^+$, requires 317.1624.

7.4.12.10 Synthesis and characterisation of (4a*R*,14b*R*)-11-methoxy-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (**4.163**)



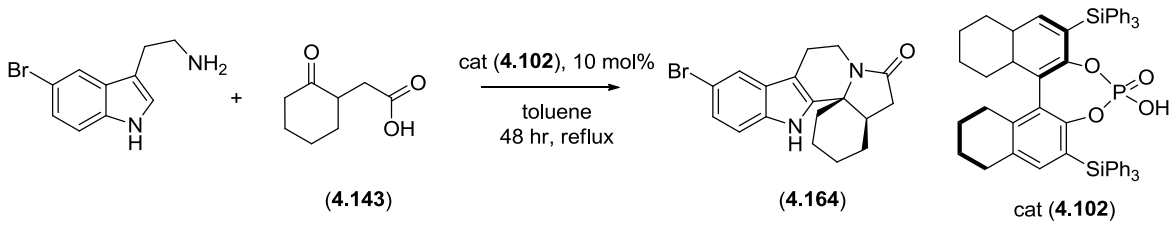
(**4.143**) (**4.163**) cat (**4.102**)

Following the general procedure the titled compound was obtained after 24 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 4 : 1) (56 mg, 90%). The ee was determined by HPLC using a Chiralpak AD column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 7.4 min, minor t_R = 11.5 min (79% ee), >98:2 dr.

M.P. 102-107 °C; **$[\alpha]_D^{25}$** = + 66.6 (c = 1.11 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3306 (br w, N-H), 1664 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.55-1.70 (m, 2H, $C\underline{H}_AH_B$, $C\underline{H}_AH_B$), 1.79-1.90 (m, 3H, $C\underline{H}_AH_B$, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$), 1.95-1.99 (m, 2H, $C(O)C\underline{H}_2CH$), 2.24-2.29 (m, 1H, $CH_A\underline{H}_B$), 2.43 (dd, 1H, *J* = 14.0 Hz, *J* = 6.3 Hz, $CH_A\underline{H}_B$), 2.51-2.62 (m, 2H, $C\underline{H}CH_2$, $CH_A\underline{H}_B$), 2.81 (dd, 1H, *J* = 15.3 Hz, *J* = 4.6 Hz, $NCH_2C\underline{H}_AH_B$), 2.90 (ddd, 1H, *J* = 15.3 Hz, *J* = 11.5 Hz, *J* = 6.4 Hz, $NCH_2CH_A\underline{H}_B$), 3.16 (td, 1H, *J* =

12.2 Hz, *J* = 5.1 Hz, NC$\underline{H}_A H_B CH_2$), 3.91 (s, 3H, C$\underline{H}_3$O), 4.49 (dd, 1H, *J* = 13.2Hz, *J* = 5.6 Hz, NC$H_A\underline{H}_B CH_2$), 6.91 (dd, 1H, *J* = 8.8 Hz, *J* = 2.5 Hz, Ar-H), 6.99 (d, 1H, *J* = 2.4 Hz, Ar-H), 7.32 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.96 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.7 ($NCH_2\underline{C}H_2$), 21.6 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 26.7 (C(O)$\underline{C}H_2$CH), 34.6 ($\underline{C}H_2$), 35.1 (N$\underline{C}H_2CH_2$), 35.9 ($\underline{C}H_2$), 38.6 ($\underline{C}HCH_2$), 56.4 ($\underline{C}H_3$O), 60.6 ($CH_2\underline{C}$N), 101.0 (Ar$\underline{C}$-H), 107.6 (Ar$\underline{C}$-quat), 112.2 (Ar$\underline{C}$-H), 112.6 (Ar$\underline{C}$-H), 127.5 (Ar$\underline{C}$-quat), 131.3 (Ar$\underline{C}$-quat), 139.4 (Ar$\underline{C}$-quat), 154.8 (Ar$\underline{C}$-quat), 173.1 (CO); ***m/z* (ES$^-$)** 309 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 333.1573 for $C_{19}H_{22}N_2ONa^+$ [M+Na]$^+$, requires 333.1573.

7.4.12.11 Synthesis and characterisation of (4a*R*,14b*R*)-11-bromo-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (**4.164**)

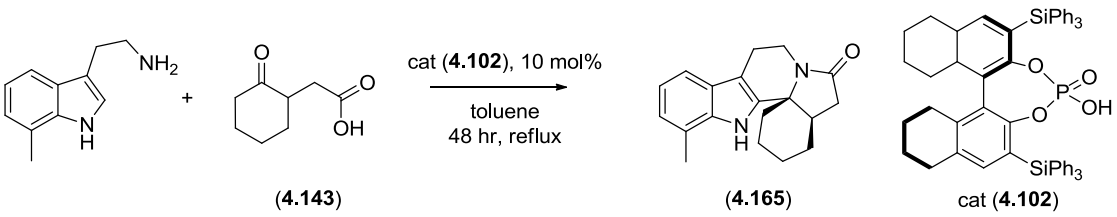


(**4.143**) (**4.164**) cat (**4.102**)

Following the general procedure the titled compound was obtained after 48 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate) (64 mg, 88%). The ee was determined by HPLC using a Chiralpak AD column (80:20 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 7.1 min, minor t_R = 21.5 min (88% ee), >98:2 dr.

M.P. 275-277 ^{o}C; **$[\alpha]_D^{25}$** = + 75.8 (c = 0.91 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3283 (br w, N-H), 1665 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.50-1.67 (m, 3H, $NCCH_2C\underline{H}_A H_B$, $NCCH_2CH_2C\underline{H}_2$), 1.74-1.87 (m, 2H, $NCC\underline{H}_A H_B CH_2$, $NCCH_2CH_A\underline{H}_B$), 1.90-1.96 (m, 2H, $CHC\underline{H}_2CH_2$), 2.17-2.25 (m, 1H, $NCCH_A\underline{H}_B CH_2$), 2.38 (dd, 1H, *J* = 12.9 Hz, *J* = 5.4 Hz, C(O)$C\underline{H}_A H_B$CH), 2.45-2.59 (m, 2H, C(O)$CH_A\underline{H}_B$CH, $C\underline{H}CH_2$), 2.71-2.88 (m, 2H, $NCH_2C\underline{H}_2$), 3.10 (td, 1H, *J* = 12.3 Hz, *J* = 5.3 Hz, $NC\underline{H}_A H_B CH_2$), 4.44 (dd, 1H, *J* = 13.2 Hz, *J* = 6.0 Hz, $NCH_A\underline{H}_B CH_2$), 7.23-7.30 (m, 2H, 2 x Ar-H), 7.62 (s, 1H, Ar-H), 8.09 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.2 ($CHCH_2\underline{C}H_2$), 20.9 ($NCH_2\underline{C}H_2$), 22.0 ($NCCH_2\underline{C}H_2$), 26.1 ($CH\underline{C}H_2CH_2$), 34.1 ($N\underline{C}H_2CH_2$), 34.5 ($NC\underline{C}H_2CH_2$), 35.4 (C(O)$\underline{C}H_2$CH), 37.9 ($\underline{C}HCH_2$), 60.1 ($CH_2\underline{C}$N), 106.9 (Ar$\underline{C}$-quat), 112.5 (Ar$\underline{C}$-H), 113.1 (Ar$\underline{C}$-quat), 121.1 (Ar$\underline{C}$-H), 124.9 (Ar$\underline{C}$-H), 128.3 (Ar$\underline{C}$-quat), 134.5 (Ar$\underline{C}$-quat), 139.3 (Ar$\underline{C}$-quat), 172.8 (CO); ***m/z* (ES$^-$)** 357, 359 ([M-H]$^-$, 70%); **HRMS ES (+)** Found 381.0573 and 383.0555 for $C_{18}H_{19}N_2OBrNa^+$ [M+Na]$^+$, requires 381.0573 and 383.0553.

7.4.12.12 Synthesis and characterisation of (4a*R*,14b*R*)-13-methyl-1,2,3,4,4a,5,9,14-octahydro-6*H*,8*H*-pyrido[3,4-*b*:1,2-*i*']diindol-6-one (**4.165**)

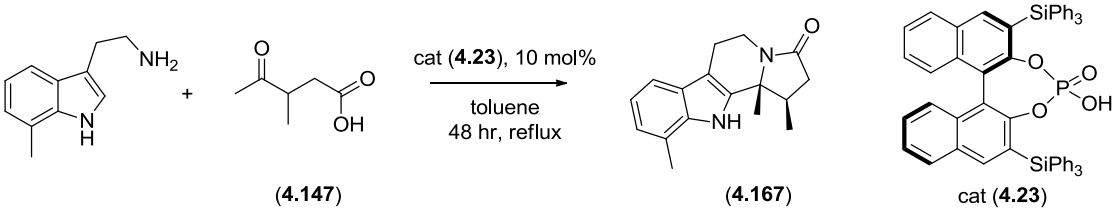


(**4.143**) (**4.165**) cat (**4.102**)

Following the general procedure the titled compound was obtained after 48 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 3 : 2) (52 mg, 89%). The ee was determined by HPLC using a Chiralpak AD column (95:5 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 10.9 min, minor t_R = 16.0 min (98% ee), >98:2 dr.

M.P. 113-117 ^{o}C; **$[\alpha]_D^{25}$** = + 24.6 (c = 0.89 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3293 (br w, N-H), 1669 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.50-1.70 (m, 2H, C$\underline{H}_A$H$_B$, C$\underline{H}_A$H$_B$), 1.76-1.88 (m, 3H, C$\underline{H}_A$H$_B$, CH$_A\underline{H}_B$, CH$_A\underline{H}_B$), 1.90-1.96 (m, 2H, C(O)C$\underline{H}_2$CH), 2.17-2.24 (m, 1H, CH$_A\underline{H}_B$), 2.35-2.44 (m, 1H, C$\underline{H}_A$H$_B$), 2.48-2.52 (m, 5H, C$\underline{H}$CH$_2$ C$\underline{H}_3$C, CH$_A\underline{H}_B$), 2.79 (dd, 1H, *J* = 15.4 Hz, *J* = 5.1 Hz, NCH$_2$C$\underline{H}_A$H$_B$), 2.84-2.93 (m, 1H, NCH$_2$CH$_A\underline{H}_B$), 3.11 (td, 1H, *J* = 12.3 Hz, *J* = 5.3 Hz, NC$\underline{H}_A$H$_B$CH$_2$), 4.44 (dd, 1H, *J* = 13.1 Hz, *J* = 6.1 Hz, NCH$_A\underline{H}_B$CH$_2$), 7.02 (d, 1H, *J* = 7.1 Hz, Ar-H,), 7.08 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.36 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.70 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 17.1 (C$\underline{H}_3$), 20.9 (C$\underline{H}_2$), 21.4 (NCH$_2$C$\underline{H}_2$), 22.4 (C$\underline{H}_2$), 27.1 (C(O)C$\underline{H}_2$CH), 34.5 (C$\underline{H}_2$), 35.3 (NC$\underline{H}_2$CH$_2$), 36.3 (C$\underline{H}_2$), 38.0 (C$\underline{H}$CH$_2$), 61.2 (CH$_2$C$\underline{N}$), 108.3 (Ar$\underline{C}$-quat), 116.5 (Ar$\underline{C}$-H), 120.5 & 120.6 (Ar$\underline{C}$-H, Ar$\underline{C}$-quat), 123.3 (Ar$\underline{C}$-H), 126.6 (Ar$\underline{C}$-quat), 135.7 (Ar$\underline{C}$-quat), 138.2 (Ar$\underline{C}$-quat), 174.5 (CO); ***m/z* (ES$^-$)** 293 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 317.1619 for $C_{19}H_{22}N_2ONa^+$ [M+Na]$^+$, requires 317.1624.

7.4.12.13 Synthesis and characterisation of (1*R*,11b*R*)-1,10,11b-trimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.167**)



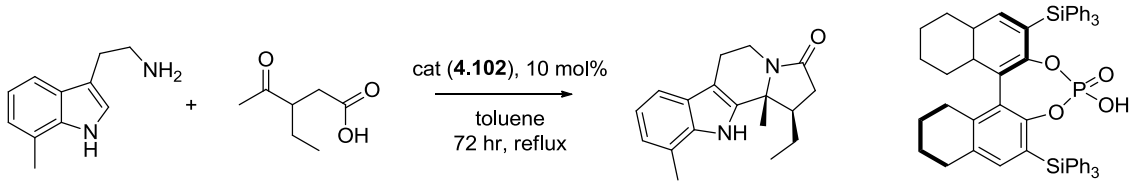
(**4.147**) (**4.167**) cat (**4.23**)

Following the general procedure the titled compound was obtained after 48 hours at reflux in the presence of (**4.23**) as a colourless crystalline solid following flash silica gel chromatography (ethyl

acetate : petroleum ether, 1 : 1) (62 mg, 95%). The ee was determined by HPLC using a Chiralpak OD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 18.0 min, major t_R = 23.2 min (95% ee), dr = 97:3.

M.P. 190-196 ^{o}C; **$[\alpha]_D^{25}$** = + 161.3 (c = 1.12 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3292 (br w, N-H), 1667 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.41 (d, 3H, *J* = 6.5 Hz, C$\underline{H}_3$CH), 1.49 (s, 3H, C$\underline{H}_3$), 2.27-2.39 (m, 1H, CH$_3$C$\underline{H}$), 2.45-2.59 (m, 5H, C(O)C$\underline{H}_2$CH, C$\underline{H}_3$), 2.80-2.85 (m, 2H, NCH$_2$C$\underline{H}_2$), 3.04 (m, 1H, N$\underline{H}_A$H$_B$CH$_2$), 4.50 (ddd, 1H, *J* = 12.9 Hz, *J* = 4.3 Hz, *J* = 2.8 Hz, NH$_A$$\underline{H}_BCH_2$), 7.02 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.08 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.37 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.03 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 15.0 (C$\underline{H}_3$CH), 16.8 (C$\underline{H}_3$), 19.3 (C$\underline{H}_3$), 21.7 (NCH$_2$C$\underline{H}_2$), 35.0 (NC$\underline{H}_2$CH$_2$), 38.8 C(O)C$\underline{H}_2$CH), 39.2 (C$\underline{H}$CH$_2$) 61.7 (CH$_3$C$\underline{N}$), 107.8 (ArC-quat), 116.2 (ArC-H), 120.2 (ArC-H), 120.3 (ArC-quat), 123.0 (ArC-H), 126.3 (ArC-quat), 135.6 (ArC-quat), 137.8 (ArC-quat), 171.9 (CO); ***m/z* (ES$^-$)** 267 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 291.1469 for $C_{17}H_{20}N_2ONa^+$ [M+Na]$^+$, requires 291.1468.

7.4.12.14 Synthesis and characterisation of (1*R*,11b*R*)-1-ethyl-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.168**)



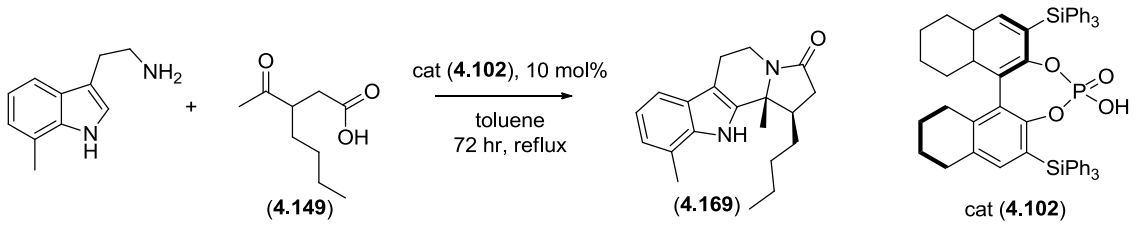
(**4.148**) (**4.168**) cat (**4.102**)

Following the general procedure the reaction was carried out on a 0.3 mmol scale. The titled compound was obtained after 54 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 3 : 2) (69 mg, 81%). The ee was determined by HPLC using a Chiralpak OD column (85:15 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 8.4 min, major t_R = 18.6 min (94% ee), dr = 97:3.

M.P. 107-111 ^{o}C; **$[\alpha]_D^{25}$** = + 161.2 (c = 1.06 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3290 (br w, N-H), 1667 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.07 (t, 3H, *J* = 7.3 Hz, C$\underline{H}_3$CH$_2$), 1.48 (s, 3H, C$\underline{H}_3$C), 1.62-1.74 (m, 1H, CH$_3$C$\underline{H}_A$H$_B$), 1.89-2.00 (m, 1H, CH$_3$CH$_A$$\underline{H}_B$), 2.23-2.36 (m, 2H, C(O)C$\underline{H}_A$H$_B$CH, C$\underline{H}$CH$_2$), 2.52 (s, 3H, C$\underline{H}_3$), 2.58-2.68 (m, 1H, C(O)CH$_A$$\underline{H}_B$CH), 2.79-2.84 (m, 2H, NCH$_2$C$\underline{H}_2$), 3.03 (dt, 1H, *J* = 13.0 Hz, *J* = 8.4 Hz, NC$\underline{H}_A$H$_B$CH$_2$), 4.50 (dt, 1H, *J* = 6.9 Hz, *J* = 3.7 Hz, NCH$_A$$\underline{H}_BCH_2$), 7.02 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.08 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.36 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.85 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 12.8 (C$\underline{H}_3$CH$_2$), 16.8 (C$\underline{H}_3$), 19.8 (C$\underline{H}_3$), 21.6 (NCH$_2$C$\underline{H}_2$), 23.7 (CH$_3$C$\underline{H}_2$), 34.8 (NC$\underline{H}_2$CH$_2$), 36.5 (C(O)C$\underline{H}_2$CH), 46.5 (C$\underline{H}$CH$_2$), 61.6 (CH$_3$C$\underline{N}$), 107.9 (ArC-quat), 116.2 (ArC-H), 120.2 (2C, ArC-H, ArC-quat), 123.0 (ArC-H), 126.2 (ArC-quat),

135.5 (ArC-quat), 137.7 (ArC-quat), 171.7 (CO); ***m/z* (ES$^-$)** 281 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 305.1626 for $C_{18}H_{22}N_2ONa^+$ $[M+Na]^+$, requires 305.1624.

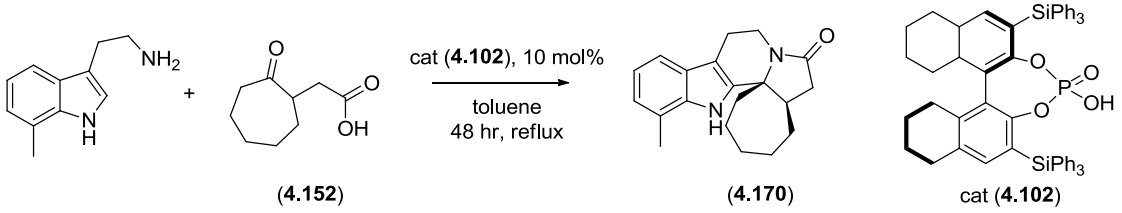
7.4.12.15 Synthesis and characterisation of (1*R*,11b*R*)-1-butyl-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.169**)



Following the general procedure the titled compound was obtained after 72 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (58 mg, 94%). The ee was determined by HPLC using a Chiralpak OD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 6.6 min, major t_R = 12.9 min (98% ee), >98:2 dr.

M.P. 208-210 ^oC; **$[\alpha]_D^{25}$** = + 100.9 (c = 0.91 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3296 (br w, N-H), 1668 (s, C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) 0.97 (t, 3H, *J* = 6.3 Hz, $C\underline{H}_3CH_2$), 1.27-1.47 (m, 4H, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$), 1.49 (s, 3H, $C\underline{H}_3$), 1.61-1.72 (m, 1H, $CHC\underline{H}_AH_BCH_2$), 1.82-1.91 (m, 1H, $CHCH_A\underline{H}_BCH_2$), 2.23-2.42 (m, 2H, $C(O)C\underline{H}_AH_BCH$, $C\underline{H}CH_2$), 2.53 (s, 3H, $C\underline{H}_3$), 2.60 (dd, 1H, *J* = 15.0 Hz, *J* = 6.9 Hz, $C(O)CH_A\underline{H}_BCH$), 2.79-2.84 (m, 2H, $NCH_2C\underline{H}_2$), 2.98-3.07 (m, 1H, $NC\underline{H}_AH_BCH_2$), 4.47-4.53 (m, 1H, $NCH_A\underline{H}_BCH_2$), 7.02 (d, 1H, *J* = 7.0 Hz, Ar-H), 7.08 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.37 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.91 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.0 ($\underline{C}H_3CH_2$), 16.8 ($\underline{C}H_3$), 19.7 (2C, $\underline{C}H_3$, $\underline{C}H_2$), 21.7 ($\underline{C}H_2$), 22.8 ($NCH_2\underline{C}H_2$), 30.4 ($CH\underline{C}H_2CH_2$), 34.9 ($N\underline{C}H_2CH_2$), 36.9 ($C(O)\underline{C}H_2CH$), 44.7 ($\underline{C}HCH_2$), 61.6 ($CH_3\underline{C}N$), 107.9 (Ar*C*-quat), 116.2 (Ar*C*-H), 120.2 (2C, Ar*C*-H, Ar*C*-quat), 123.0 (Ar*C*-H), 126.2 (Ar*C*-quat), 135.5 (Ar*C*-quat), 137.8 (Ar*C*-quat), 171.7 (CO); ***m/z* (ES$^-$)** 309 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 333.1937 for $C_{20}H_{26}N_2ONa^+$ $[M+Na]^+$, requires 333.1937.

7.4.12.16 Synthesis and characterisation of (5a*R*,15b*R*)-14-methyl-2,3,4,5,5a,6,10,15-octahydro-9*H*-cyclohepta[1,8a]indolizino[8,7-*b*]indol-7(1*H*)-one (**4.170**)

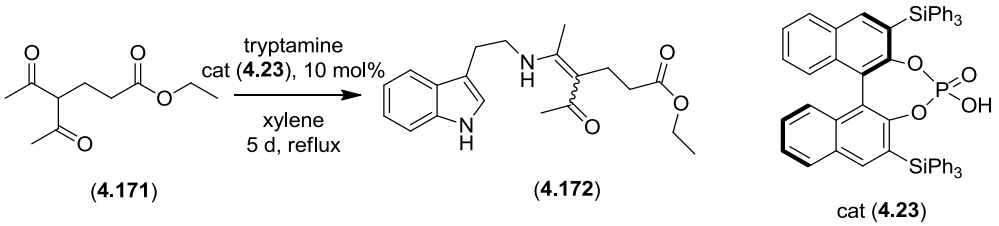


Following the general procedure the reaction was carried out on a 0.3 mmol scale. The titled compound was obtained after 48 hours at reflux in the presence of (**4.102**) as a colourless crystalline solid following flash silica gel chromatography (ethyl acetate : petroleum ether, 1 : 1) (84 mg, 91%). The ee was determined by HPLC using a Chiralpak AD column (90:10 hexane/isopropanol) flow rate 1 ml/min, 220 nm, major t_R = 7.5 min, minor t_R = 9.9 min (93% ee), >98:2 dr.

M.P. 128-133 ^{o}C; **$[\alpha]_D^{25}$** = + 15.1 (c = 0.67 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3279 (br w, N-H), 1662 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.46-1.58 (m, 2H, C$\underline{H}_2$), 1.69-1.76 (m, 1H, C$\underline{H}_A$H$_B$), 1.80-1.88 (m, 2H, C$\underline{H}_2$), 1.90-1.96 (m, 1H, C$\underline{H}_A$H$_B$), 2.03-2.13 (m, 3H, C$\underline{H}_2$, CH$_A\underline{H}_B$), 2.28 (dd, 1H, *J* = 15.1 Hz, *J* = 8.8 Hz, CH$_A\underline{H}_B$), 2.49-2.55 (m, 4H, C(O)C$\underline{H}_A$H$_B$CH, C$\underline{H}_3$) 2.68-2.79 (m, 2H, NCH$_2$C$\underline{H}_A$H$_B$, C(O)CH$_A\underline{H}_B$CH), 2.92-3.01 (m, 2H, NCH$_2$CH$_A\underline{H}_B$, H-7), 3.15 (td, 1H, *J* = 12.5 Hz, *J* = 4.7 Hz, NC$\underline{H}_A$H$_B$CH$_2$), 4.56 (dd, 1H, *J* = 13.2 Hz, *J* = 6.3 Hz, NCH$_A\underline{H}_B$CH$_2$), 7.05 (d, 1H, *J* = 6.9 Hz, Ar-H), 7.10 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.38 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.90 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 17.2 (C$\underline{H}_3$), 21.4 (NCH$_2$C$\underline{H}_2$), 23.9 (C$\underline{H}_2$), 25.3 (C$\underline{H}_2$), 30.3 (C$\underline{H}_2$), 31.5 (C$\underline{H}_2$), 35.5 & 35.8 (NC$\underline{H}_2$CH$_2$, C(O)C$\underline{H}_2$CH), 38.5 (C$\underline{H}_2$), 41.6 (C$\underline{H}$CH$_2$), 66.9 (CH$_2$C$\underline{N}$), 107.7 (Ar$\underline{C}$-quat), 116.6 (Ar$\underline{C}$-H), 120.6 (2C, Ar$\underline{C}$-H, Ar$\underline{C}$-quat), 123.3 (Ar$\underline{C}$-H), 126.7 (Ar$\underline{C}$-quat), 135.8 (Ar$\underline{C}$-quat), 139.8 (Ar$\underline{C}$-quat), 174.1 (CO); ***m/z* (ES$^-$)** 307 ([M-H]$^-$, 100%); **HRMS ES (+)** Found 331.1780 for $C_{20}H_{24}N_2ONa^+$ [M+Na]$^+$, requires 331.1781.

7.4.13 Attempt at *δ*-lactam formation

7.4.13.1 Synthesis and characterisation of ethyl 4-acetyl-5-{[2-(1*H*-indol-3-yl)ethyl]amino}hex-4-enoate (**4.172**)



Ethyl 4-acetyl-5-oxohexanoate (**4.171**) (38 µL, 0.2 mmol) was dissolved in xylene (42 mL) and tryptamine (32 mg, 0.2 mmol) was added in one portion at room temperature, immediately followed by the addition of phosphoric acid catalyst (**4.23**) (17.3 mg, 0.02 mmol) in one portion. The resulting suspension was heated under reflux for 5 days. The solvent was removed *in vacuo*, and the residue purified by chromatography on silica gel (ethyl acetate : petroleum ether, 1 : 1) to yield a colourless crystalline solid (25 mg, 37%).

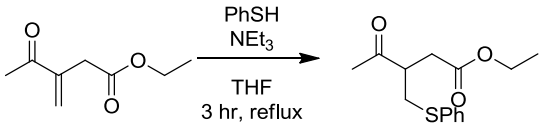
M.P. 65-69 **ºC**; **ν_{max}(film)/cm^{-1}** 3234 (br w, N-H), 1729 (s, C=O), 1593 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.26 (t, 3H, *J* = 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.94 (s, 3H, C$\underline{H}_3$), 2.16 (s, 3H, C$\underline{H}_3$), 2.27-2.33 (m, 2H, C$\underline{H}_2$), 2.54-2.60 (m, 2H, C$\underline{H}_2$), 3.06 (t, 2H, *J* = 6.8 Hz, NCH$_2$C$\underline{H}_2$), 3.55-3.62 (m, 2H, NC$\underline{H}_2$CH$_2$), 4.13 (q, 2H, *J* = 7.1 Hz, C$\underline{H}_2$CH$_3$), 7.09-7.14 (m, 2H, NHC$\underline{H}$, Ar-H), 7.18 (t, 1H, *J* = 7.5 Hz, Ar-H),

7.34 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.57 (br s, 1H, N-H), 12.24 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.2 ($CH_2\underline{C}H_3$), 14.9 ($\underline{C}H_3$), 24.9 ($\underline{C}H_2$), 26.0 ($NCH_2\underline{C}H_2$), 27.4 ($\underline{C}H_3$), 35.8 ($\underline{C}H_2$), 44.1 ($N\underline{C}H_2CH_2$), 60.4 ($\underline{C}H_2CH_3$), 101.9 (C-quat), 111.4 (Ar$\underline{C}$-H), 112.1 (C-quat), 118.4 (Ar$\underline{C}$-H), 119.3 & 121.9 & 122.9 (2 x Ar$\underline{C}$-H, NH$\underline{C}$H), 127.0 (Ar$\underline{C}$-quat), 136.4 (Ar$\underline{C}$-quat), 163.2 (Ar$\underline{C}$-quat), 173.2 (CO), 194.2 (CO); ***m/z* (ES$^+$)** 365 ($[M+Na]^+$, 30%), 707 ($[2M+Na]^+$, 100%); **HRMS ES (+)** Found 365.1830 for $C_{20}H_{26}N_2O_3Na^+$ $[M+Na]^+$, requires 365.1836.

7.5 Experimental for chapter 5

7.5.1 Studies towards the synthesis of ketone (**4.84**)

7.5.1.1 Synthesis and characterisation of ethyl 4-oxo-3-[(phenylthio)methyl]pentanoate (**5.10**)

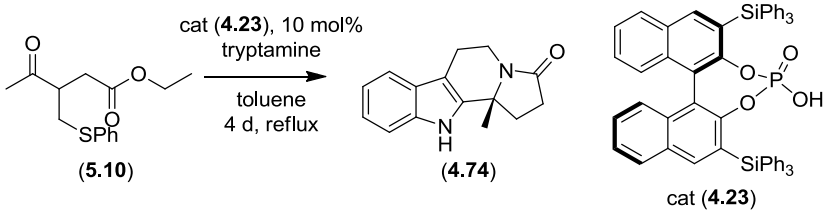


(**4.94**) (**5.10**)

To a solution of PhSH (51 µL, 0.7 mmol) in anhydrous THF (3 mL) at 0 ºC under N_2 was added NEt_3 (9 µL, 0.06 mmol) and a solution of alkene (**4.94**) (100 mg, 0.64 mmol) in THF (3 mL) under N_2 and the solution was heated to reflux for 3 hours before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (ethyl acetate : petroleum ether, 4 : 1) afforded the titled compound as a colourless oil (143 mg, 84%).

ν_{max}(film)/cm^{-1} 1731 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.23 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.25 (s, 3H, C(O)C$\underline{H}_3$), 2.58-2.64 (m, 1H, C$\underline{H}$H), 2.80 (dd, 1H, *J* = 16.9 Hz, *J* = 8.6 Hz, C$\underline{H}$H), 2.89-2.98 (m, 1H, C$\underline{H}$H), 3.13-3.23 (m, 2H, C$\underline{H}$H, C$\underline{H}CH_2$), 4.10 (q, 2H, *J* = 7.1 Hz, C$\underline{H}_2CH_3$), 7.20-7.40 (m, 5H, 5 x Ar-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 30.2 (C(O)$\underline{C}H_3$), 35.1 ($\underline{C}H_2$), 35.2 ($\underline{C}H_2$), 47.2 ($\underline{C}HCH_2$), 60.8 ($\underline{C}H_2CH_3$), 126.8 (Ar$\underline{C}$-H), 129.2 (2 x Ar$\underline{C}$-H), 130.0 (2 x Ar$\underline{C}$-H), 135.1 (S$\underline{C}$CH), 171.8 (CO), 209.0 (CO); ***m/z* (ES$^+$)** 289 ([M+Na]$^+$, 55%), 555 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 289.0868 for $C_{14}H_{18}O_3SNa^+$ [M+Na]$^+$, requires 289.0869.

7.5.1.2 Synthesis and characterisation of (11b*R*)-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (**4.74**)[78]



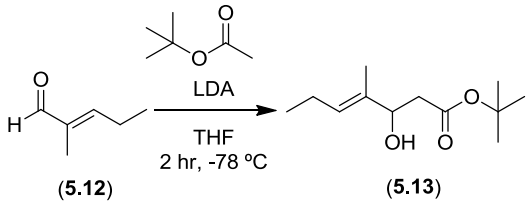
(**5.10**) (**4.74**) cat (**4.23**)

To a solution of (**5.10**) (53 mg, 0.2 mmol) in toluene (42 mL), was added tryptamine (32 mg, 0.2 mmol) and catalyst (**4.23**) (17 mg, 0.02 mmol) and the solution was refluxed for 4 days before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (ethyl acetate) afforded the titled compound as a colourless solid (25 mg, 51%). The ee was determined by HPLC using a Chiralpak OD column (80:20 hexane/isopropanol) flow rate 2 ml/min, 220 nm, major t_R = 3.7 min, minor t_R = 4.4 min (60% ee).

M.P. 214-219 ^{o}C; **$[\alpha]_D^{25}$** = + 17.2 (c = 0.80 in $CHCl_3$) (lit. **$[\alpha]_D^{23}$** = + 179.0 (c = 1.0 in $CHCl_3$), 96% ee); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.60 (s, 3H, C$\underline{H}_3$C), 2.13-2.23 (m, 1H, C$\underline{H}_A$H$_B$CH$_2$C(O)), 2.29 (ddd, 1H, *J* = 11.0 Hz, *J* = 8.9 Hz, *J* = 2.0 Hz, CH$_A\underline{H}_B$CH$_2$C(O)), 2.47 (ddd, 1H, *J* = 16.8 Hz, *J* = 9.5

Hz, *J* = 2.0 Hz, C$\underline{H}_A$H$_B$C(O)), 2.62-2.73 (m, 1H, CH$_A\underline{H}_B$C(O)), 2.77-2.90 (m, 2H, NCH$_2$C$\underline{H}_2$C), 3.06-3.15 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$C), 4.45-4.51 (m, 1H, NCH$_A\underline{H}_B$CH$_2$C), 7.13 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.19 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.34 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.43 (br s, 1H, N-H); ***m/z* (ES$^+$)** 263 ([M+Na]$^+$, 30%), 503 ([2M+Na]$^+$, 100%).

7.5.1.3 Synthesis and characterisation of *tert*-butyl (4*E*)-3-hydroxy-4-methylhept-4-enoate (**5.13**)

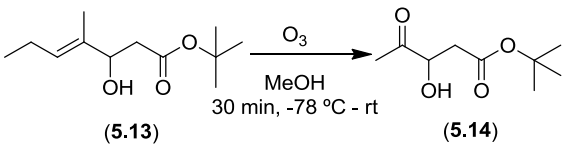


(**5.12**) (**5.13**)

A procedure developed by Kobayashi *et al.* was followed.[94] To a solution of *tert*-butyl acetate (2.46 mL, 18.3 mmol) in THF (10 mL) at -78 ºC under N_2 was added a solution of LDA in THF (30 mL, 18.3 mmol). The solution was stirred at -78 ºC for 30 minutes before the addition of alkene (**5.12**) (1.16 mL, 10.2 mmol) in THF (10 mL) at -78 ºC. The solution was stirred at -78 ºC for 2 hours before quenching with a saturated solution of NH_4Cl (5 mL) and warming to room temperature. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent evaporated *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (petroleum ether : ethyl acetate, 7 : 3) afforded the titled compound as a colourless oil (2.16 g, 99%).

ν_{max}(film)/cm^{-1} 3438 (br m, O-H), 2968 (s, C-H alkene), 1730 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 0.93 (t, 3H, *J* = 7.6 Hz, CH$_2$C$\underline{H}_3$), 1.43 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.60 (s, 3H, C$\underline{H}_3$C), 1.94-2.07 (m, 2H, C$\underline{H}_2$CH$_3$), 2.37-2.51 (m, 2H, C(O)C$\underline{H}_2$), 3.00 (br s, 1H, O-H), 4.35 (dd, 1H, *J* = 8.6 Hz, *J* = 4.1 Hz, C(O)CH$_2$C$\underline{H}$), 5.43 (t, 1H, *J* = 7.0 Hz, CH$_3$CH$_2$C$\underline{H}$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 11.6 (C$\underline{H}_3$C), 13.9 (CH$_2$C$\underline{H}_3$), 20.8 (C$\underline{H}_2$CH$_3$), 28.0 (C(C$\underline{H}_3$)$_3$), 41.2 (C(O)C$\underline{H}_2$), 73.5 (C(O)CH$_2$C$\underline{H}$), 81.1 (C-quat), 128.4 (CH$_3$CH$_2$C$\underline{H}$), 134.6 (C-quat), 172.1 (CO); ***m/z* (ES$^+$)** 237 ([M+Na]$^+$, 50%), 451 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 237.1459 for $C_{12}H_{22}O_3Na^+$ [M+Na]$^+$, requires 237.1461.

7.5.1.4 Synthesis and characterisation of *tert*-butyl 3-hydroxy-4-oxopentanoate (**5.14**)

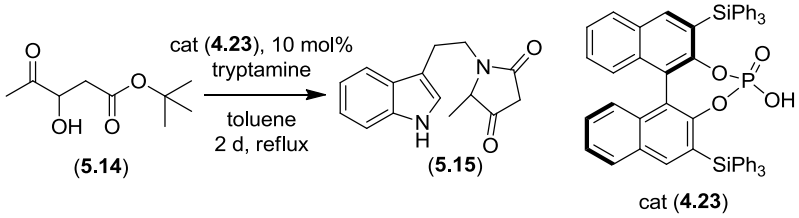


(**5.13**) (**5.14**)

A procedure developed by Kobayashi *et al.* was followed.[94] O_3 was bubbled through a solution of alkene (**5.13**) (1.0 g, 4.66 mmol) in MeOH (35 mL) at -78 ºC for 30 minutes before quenching with DMS (685 µL, 9.33 mmol). The solution was slowly warmed to room temperature and allowed to stir at room temperature for 2 hours before adding more DMS (3.42 mL, 46.6 mmol) and stirring for 12 hours. The solution was evaporated *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (petroleum ether : ethyl acetate, 3 : 2) afforded the titled compound as a colourless oil (822 mg, 95%).

ν_{max}(film)/cm^{-1} 3467 (m, O-H), 1723 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.45 (s, 9H, $C(C\underline{H}_3)_3$), 2.28 (s, 3H, $C(O)C\underline{H}_3$), 2.71 (dd, 1H, *J* = 16.3 Hz, *J* = 5.6 Hz, $C(O)C\underline{H}_AH_B$), 2.79 (dd, 1H, *J* = 16.3 Hz, *J* = 4.5 Hz, $C(O)CH_A\underline{H}_B$), 3.81 (br s, 1H, O-H), 4.31 (app. t, 1H, *J* = 5.0 Hz, $C(O)CH_2C\underline{H}$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 25.3 ($C(O)\underline{C}H_3$), 28.0 ($C(\underline{C}H_3)_3$), 39.2 ($C(O)\underline{C}H_2$), 74.0 ($C(O)CH_2\underline{C}H$), 82.0 ($\underline{C}(CH_3)_3$), 170.0 (CO), 208.5 (CO); ***m/z* (ES$^+$)** 211 ([M+Na]$^+$, 50%), 399 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 211.0939 for $C_9H_{16}O_4Na^+$ [M+Na]$^+$, requires 211.0941.

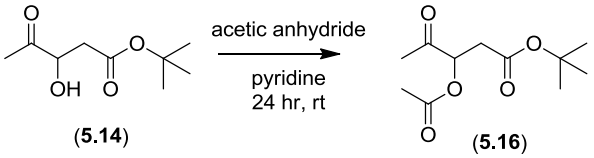
7.5.1.5 Synthesis and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]-5-methylpyrrolidine-2,4-dione (**5.15**)



To a solution of (**5.14**) (37 mg, 0.2 mmol) in toluene (42 mL), was added tryptamine (32 mg, 0.2 mmol) and catalyst (**4.23**) (17 mg, 0.02 mmol) and the solution was refluxed for 2 days before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (dichloromethane : acetone, 9 : 1) afforded the titled compound as a colourless solid (22 mg, 43%).

M.P. 116-118 ºC; **$[\alpha]_D^{25}$** = + 7.0 (c = 1.86 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3294 (w, N-H), 1770 (w, C=O), 1677 (s, C=O); **^{1}H NMR: δ_H** (500 MHz, $CDCl_3$) 1.28 (d, 3H, *J* = 7.0 Hz, $C\underline{H}_3CH$), 3.00-3.07 (m, 3H, $C(O)C\underline{H}_2$, $NCH_2C\underline{H}_AH_B$), 3.15 (ddd, 1H, *J* = 14.7 Hz, *J* = 8.3 Hz, *J* = 6.5 Hz, $NCH_2CH_A\underline{H}_B$), 3.36-3.43 (m, 1H, $NC\underline{H}_AH_BCH_2$), 3.78 (q, 1H, *J* = 7.0 Hz, $C\underline{H}CH_3$), 4.13-4.21 (m, 1H, $NCH_A\underline{H}_BCH_2$), 7.06 (d, 1H, *J* = 1.8 Hz, $NHC\underline{H}$), 7.12-7.16 (m, 1H, Ar-H), 7.19-7.23 (m, 1H, Ar-H), 7.37 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.62 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.19 (br s, 1H, N-H); **^{13}C NMR: δ_C** (125 MHz, $CDCl_3$) 15.3 ($\underline{C}H_3CH$), 23.3 ($NCH_2\underline{C}H_2$), 40.6 & 40.7 ($C(O)\underline{C}H_2$, $N\underline{C}H_2CH_2$), 62.8 ($CH_3\underline{C}H$), 111.4 (Ar$\underline{C}$-H), 112.4 (Ar$\underline{C}$-quat), 118.3 (Ar$\underline{C}$-H), 119.6 (Ar$\underline{C}$-H), 121.9 & 122.3 (Ar$\underline{C}$-H, NH$\underline{C}$H), 127.2 (Ar$\underline{C}$-quat), 136.3 (Ar$\underline{C}$-quat), 168.4 (CO), 207.0 (CO); ***m/z* (ES$^+$)** 279 ([M+Na]$^+$, 70%), 535 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 279.1103 for $C_{15}H_{16}N_2O_2Na^+$ [M+Na]$^+$, requires 279.1104.

7.5.1.6 Synthesis and characterisation of *tert*-butyl 3-acetoxy-4-oxopentanoate (**5.16**)

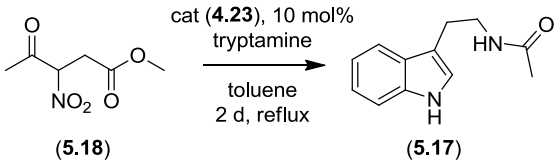


To a solution of alcohol (**5.14**) (172 mg, 0.92 mmol) in pyridine (4 mL) under N_2 was added acetic anhydride (157 µL, 1.66 mmol) and the solution was stirred at room temperature for 24 hours before diluting with EtOAc (10 mL) and adding a saturated solution of $CuSO_4$ (10 mL). The organic

layer was washed with a saturated solution of $CuSO_4$ (3 x 10 mL) before drying over Na_2SO_4 and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (petroleum ether : diethyl ether, 3 : 2) afforded the titled compound as a colourless oil (210 mg, 99%).

ν_{max}(film)/cm^{-1} 1731 (br s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.43 (s, 9H, C(C$\underline{H}_3$)$_3$), 2.14 (s, 3H, C$\underline{H}_3$), 2.21 (s, 3H, C$\underline{H}_3$), 2.72-2.75 (m, 2H, C(O)C$\underline{H}_2$), 5.34 (t, 1H, *J* = 5.9 Hz, C(O)CH$_2$C$\underline{H}$); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 20.6 (C$\underline{H}_3$), 26.4 (C$\underline{H}_3$), 27.9 (C(C$\underline{H}_3$)$_3$), 36.8 (C(O)C$\underline{H}_2$), 74.8 (C(O)CH$_2$C$\underline{H}$), 81.7 (C(CH$_3$)$_3$), 168.5 (CO), 170.1 (CO), 204.5 (CO); ***m/z* (ES$^+$)** 253 ([M+Na]$^+$, 40%), 483 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 253.1045 for $C_{11}H_{18}O_5Na^+$, [M+Na]$^+$, requires 253.1046.

7.5.1.7 Synthesis and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (**5.17**)[95]



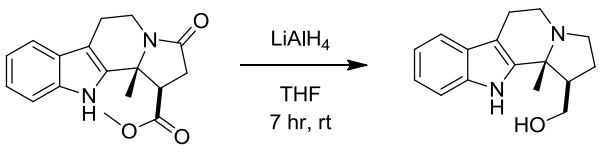
(**5.18**) (**5.17**)

To a solution of β-nitroester (**5.18**) (35 mg, 0.2 mmol) in toluene (42 mL), was added tryptamine (32 mg, 0.2 mmol) and catalyst (**4.23**) (17 mg, 0.02 mmol) and the solution was refluxed for 2 days before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (increasing polarity from dichloromethane : acetone, 9 : 1 to 4 : 1) afforded the titled compound as a colourless oil (23 mg, 58%).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 1.97 (s, 3H, C(O)C$\underline{H}_3$), 3.03 (t, 2H, *J* = 6.8 Hz, NHCH$_2$C$\underline{H}_2$), 3.65 (app. q, 2H, *J* = 6.6 Hz, NHC$\underline{H}_2$CH$_2$), 5.66 (br s, 1H, N$\underline{H}$CH$_2$), 7.08 (d, 1H, *J* = 2.4 Hz, NHC$\underline{H}$), 7.16-7.21 (m, 1H, Ar-H), 7.24-7.29 (m, 1H, Ar-H), 7.43 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.65 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.38 (br s, 1H, N-H); ***m/z* (ES$^+$)** 225 ([M+Na]$^+$, 95%).

7.5.2 Studies towards subincanadine B from methyl ester (±)-(**4.116**)

7.5.2.1 Synthesis and characterisation of (±)-(11b-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)methanol (±)-(**5.20**)



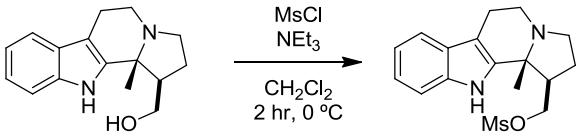
(±)-(**4.116**) (±)-(**5.20**)

To a solution of methyl ester (±)-(**4.116**) (500 mg, 1.67 mmol) in THF (16 mL) at -10 ºC under N_2 was added $LiAlH_4$ (6.7 mL, 6.70 mmol, 1.0 M sol. in THF) and the solution was stirred at room temperature for 7 hours before cooling to 0 ºC and adding $Na_2SO_4 \cdot 10H_2O$. The solution was stirred

at room temperature for 10 minutes and then filtered through a celite pad to remove the salts. The solvent was evaporated *in vacuo* to afford the crude (425 mg, 99%) which did not require further purification.

M.P. 195-197 ºC; **ν_{max}(film)/cm^{-1}** 3397 (br w, N-H, OH); **^{1}H NMR: δ_H** (400 MHz, CD_3OD) 1.47 (s, 3H, C$\underline{H}_3$C), 1.56-1.66 (m, 1H, C$\underline{H}_A$H$_B$CHCH$_2$OH), 1.86-1.95 (m, 1H, CH$_A\underline{H}_B$CHCH$_2$OH), 2.39-2.48 (m, 1H, C$\underline{H}$CH$_2$OH), 2.54-2.61 (dt, 1H, *J* = 15.7 Hz, *J* = 3.2 Hz, C$\underline{H}_A$H$_B$), 2.87-2.97 (m, 3H, NC$\underline{H}_2$CH$_2$CH, CH$_A\underline{H}_B$), 3.16-3.21 (m, 2H, C$\underline{H}_2$), 3.70 (dd, 1H, *J* = 10.4 Hz, *J* = 7.1 Hz, CHC$\underline{H}_A$H$_B$OH), 3.92 (dd, 1H, *J* = 10.4 Hz, *J* = 7.9 Hz, CHCH$_A\underline{H}_B$OH), 6.97 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.04 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.29 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.39 (d, 1H, *J* = 7.8 Hz, Ar-H); **^{13}C NMR: δ_C** (100 MHz, CD_3OD) 16.7 (C$\underline{H}_2$), 20.8 (C$\underline{H}_3$), 27.0 (C$\underline{H}_2$), 43.4 (C$\underline{H}_2$), 48.3 (NC$\underline{H}_2$CH$_2$CH), 49.6 (NCH$_2$CH$_2$C$\underline{H}$), 61.3 (CH$_3$C$\underline{H}$), 62.5 (C$\underline{H}_2$OH), 104.8 (ArC-quat), 110.8 (ArC-H), 117.8 (ArC-H), 118.7 (ArC-H), 121.0 (ArC-H), 127.2 (ArC-quat), 136.7 (ArC-quat), 140.1 (ArC-quat); ***m/z* (ES$^+$)** 257 ([M+H]$^+$, 100%); **HRMS ES (+)** Found 257.1648 for $C_{16}H_{21}N_2O$+ [M+H]$^+$, requires 257.1648.

7.2.2.2 Synthesis and characterisation of (±)-(11b-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)methyl methanesulfonate (±)-(**5.23**)

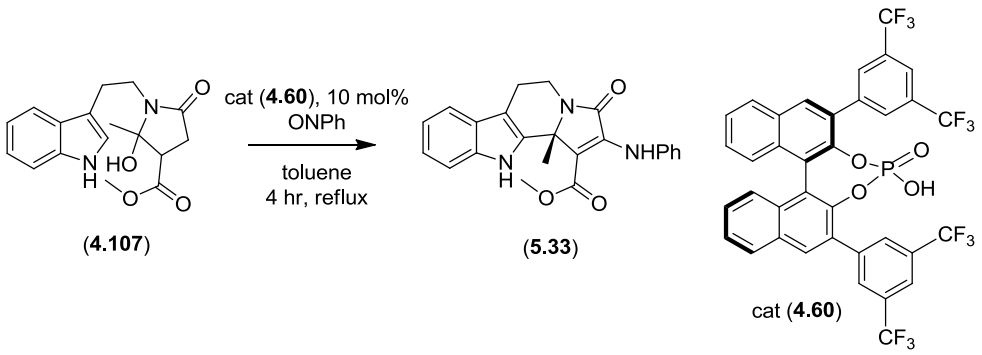


(±)-(**5.20**) (±)-(**5.23**)

To a solution of alcohol (±)-(**5.20**) (100 mg, 0.39 mmol) in CH_2Cl_2 (18 mL) at 0 ºC was added MsCl (45 µL, 0.59 mmol) and NEt_3 (98 µL, 0.70 mmol) and the solution was stirred at 0 ºC for 2 hours. CH_2Cl_2 (10 mL) and a saturated solution of NH_4Cl (20 mL) were added and the solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated *in vacuo* to afford the crude as a colourless solid (129 mg, 99%) which did not require further purification.

M.P. 50-52 ºC; **ν_{max}(film)/cm^{-1}** 3447 (br w, N-H), 1349 (br s, S=O), 1174 (br s, S-O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.53 (s, 3H, C$\underline{H}_3$C), 1.56-1.66 (m, 1H, NCH$_2$C$\underline{H}_A$H$_B$CH) 1.88-1.95 (m, 1H, NCH$_2$CH$_A\underline{H}_B$CH), 2.55-2.62 (m, 1H, NCH$_2$C$\underline{H}_A$H$_B$C), 2.67-2.76 (m, 1H, NCH$_2$CH$_2$C$\underline{H}$), 2.90-3.02 (m, 3H, NCH$_2$CH$_A\underline{H}_B$C, NC$\underline{H}_2$CH$_2$CH), 3.13 (s, 3H, OSO$_2$C$\underline{H}_3$), 3.20-3.30 (m, 2H, NC$\underline{H}_2$CH$_2$C), 4.44-4.48 (m, 2H, OC$\underline{H}_2$CH), 7.10 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.17 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.36 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.27 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 16.5 (NCH$_2$C$\underline{H}_2$C), 22.5 (C$\underline{C}$H$_3$), 26.8 (NCH$_2\underline{C}$H$_2$CH), 37.7 (OSO$_2\underline{C}$H$_3$), 42.9 (N$\underline{C}$H$_2$CH$_2$C), 47.4 (NCH$_2$CH$_2\underline{C}$H), 48.3 (N$\underline{C}$H$_2$CH$_2$CH), 60.2 (CH$_3\underline{C}$), 71.1 (O$\underline{C}$H$_2$CH), 106.2 (Ar$\underline{C}$-quat), 111.1 (Ar$\underline{C}$-H), 118.2 (Ar$\underline{C}$-H), 119.3 (Ar$\underline{C}$-H), 121.7 (Ar$\underline{C}$-H), 126.8 (Ar$\underline{C}$-quat), 135.9 (Ar$\underline{C}$-quat), 139.1 (Ar$\underline{C}$-quat); ***m/z* (ES$^+$)** 335 ([M+H]$^+$, 80%); **HRMS ES (+)** Found 335.1417 for $C_{17}H_{23}N_2O_3S^+$ [M+H]$^+$, requires 335.1424.

7.5.2.3 Synthesis and characterisation of methyl (11b*R*)-2-anilino-11b-methyl-3-oxo-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole-1-carboxylate (**5.33**)

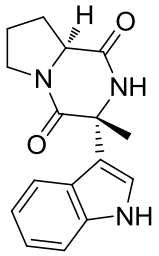


(**4.107**) (**5.33**)

To a solution of (**4.107**) (95 mg, 0.3 mmol) in toluene (63 mL), was added nitrosobenzene (96 mg, 0.9 mmol) and catalyst (**4.60**) (23 mg, 0.03 mmol) and the solution was refluxed for 4 hours before cooling and evaporating the solvent *in vacuo* to afford the crude. Purification of the crude residue by flash silica gel chromatography (increasing polarity from petroleum ether : ethyl acetate, 9 : 1 to 4 : 1) afforded the titled compound as a colourless solid (44 mg, 37%). The ee was determined by HPLC using a Chiralpak AS column (85:15 hexane/isopropanol) flow rate 1 ml/min, 220 nm, minor t_R = 9.5 min, major t_R = 13.0 min (44% ee).

M.P. 147-152 ºC; **$[\alpha]_D^{25}$** = + 48.1 (c = 1.28 in $CHCl_3$); **ν_{max}(film)/cm^{-1}** 3387 (br w, N-H), 1702 (s, C=O), 1675 (s, C=O); **^{1}H NMR: δ_H** (400 MHz, $CDCl_3$) 1.87 (s, 3H, C$\underline{H_3}$C), 2.83-3.00 (m, 2H, NCH$_2$C$\underline{H_2}$), 3.39 (ddd, 1H, *J* = 12.9 Hz, *J* = 11.6 Hz, *J* = 5.3 Hz, NC$\underline{H_A}$H$_B$CH$_2$), 3.66 (s, 3H, OC$\underline{H_3}$), 4.66 (app. dd, 1H, *J* = 12.9 Hz, *J* = 6.0 Hz, NCH$_A\underline{H_B}$CH$_2$), 7.05-7.24 (m, 5H, 5 x Ar-H), 7.31 (t, 2H, *J* = 7.7 Hz, 2 x Ar-H), 7.40 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.50 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.59 (br s, 1H, N-H), 9.59 (br s, 1H, N-H); **^{13}C NMR: δ_C** (100 MHz, $CDCl_3$) 21.5 (NCH$_2\underline{C}$H$_2$), 25.9 ($\underline{C}$H$_3$C), 36.2 (N$\underline{C}$H$_2$CH$_2$), 51.5 (O$\underline{C}$H$_3$), 60.9 (CH$_3\underline{C}$), 105.8 (C-quat), 110.7 (C-quat), 111.3 (Ar$\underline{C}$-H), 118.6 (Ar$\underline{C}$-H), 119.5 (Ar$\underline{C}$-H), 122.2 (Ar$\underline{C}$-H), 122.9 (2 x Ar$\underline{C}$-H), 125.1 (Ar$\underline{C}$-H), 126.4 (C-quat), 128.5 (2 x Ar$\underline{C}$-H), 135.6 (C-quat), 138.9 (2 x C-quat), 141.3 (C-quat), 164.2 (CO), 165.8 (CO); ***m/z* (ES$^+$)** 410 ([M+Na]$^+$, 55%), 797 ([2M+Na]$^+$, 100%); **HRMS ES (+)** Found 410.1481 for $C_{23}H_{21}N_3O_3Na^+$ [M+Na]$^+$, requires 410.1475.

Appendix 1: Crystallographic data for (2.54)



(**2.54**)

Data obtained at School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

Refinement:

The structure was solved by the direct methods. All non-H atoms were refined anisotropically. H atoms were included in calculated positions, except those bonded to the N atoms, which were found by difference Fourier techniques and refined isotropically.

Experimental:

Crystal data

$C_{16}H_{17}N_3O_2$	V = 1326.0 (4) Å^3
M_r = 283.33	Z = 4
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 6.6240 (11) Å	μ = 0.10 mm^{-1}
b = 7.5141 (12) Å	T = 100 K
c = 26.640 (4) Å	0.45 × 0.40 × 0.40 mm

Data collection

CCD area detector diffractometer	1462 reflections with $I > 2\sigma(I)$
7708 measured reflections	R_{int} = 0.039
1609 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.030	0 restraints
$wR(F^2)$ = 0.070	H atoms treated by a mixture of independent and constrained refinement
S = 1.02	$\Delta\rho_{max}$ = 0.17 e Å^{-3}
1609 reflections	$\Delta\rho_{min}$ = −0.18 e Å^{-3}
199 parameters	

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*

N1—H1*N*···O1^{i}	0.90 (2)	2.16 (2)	3.031 (2)	163.5 (19)

Data collection: Bruker *SMART*; cell refinement: Bruker *SMART*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

References:

Bruker (2001). *SMART* (Version 5.625), *SADABS* (Version 2.03a) and *SHELXTL* (Version 6.12). Bruker AXS Inc., Madison, Wisconsin, USA.

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Sheldrick, G. M. (2005). CELL_NOW. University of Göttingen, Germany.

Sheldrick, G. M. (2007). TWINABS. University of Göttingen, Germany.

Spek, A. L. (2003). J.Appl.Cryst. 36, 2003, 7-13.

Crystal data:

$C_{16}H_{17}N_3O_2$	D_x = 1.419 Mg m^{-3}
M_r = 283.33	Mo *K*α radiation, λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 891 reflections
a = 6.6240 (11) Å	θ = 2.8–26.1°
b = 7.5141 (12) Å	μ = 0.10 mm^{-1}
c = 26.640 (4) Å	*T* = 100 K
V = 1326.0 (4) Å^3	Prismatic, Colourless
Z = 4	0.45 × 0.40 × 0.40 mm
F(000) = 600	

Data collection:

CCD area detector diffractometer	1462 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.039
graphite	θ_{max} = 26.4°, θ_{min} = 2.8°
phi and ω scans	*h* = −7→8
7708 measured reflections	*k* = −9→9
1609 independent reflections	*l* = −25→33

Refinement:

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.030	Hydrogen site location: Inferred from neighbouring sites

$wR(F^2)$ = 0.070	H atoms treated by a mixture of independent and constrained refinement
S = 1.02	$w = 1/[\sigma^2(F_o^2) + (0.0402P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
1609 reflections	$(\Delta/\sigma)_{max}$ = 0.001
199 parameters	$\Delta\rho_{max}$ = 0.17 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Special details:

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.2982 (2)	0.60524 (16)	0.99067 (5)	0.0180 (3)
O2	0.87722 (19)	0.29889 (17)	0.88890 (5)	0.0189 (3)
N1	0.5748 (2)	0.6367 (2)	0.94178 (6)	0.0149 (3)
H1N	0.622 (3)	0.729 (3)	0.9596 (8)	0.025 (6)*
N2	0.5493 (2)	0.2922 (2)	0.91212 (5)	0.0142 (3)
N3	0.4163 (3)	0.7607 (2)	0.79123 (6)	0.0180 (4)
H3N	0.314 (3)	0.818 (3)	0.7787 (7)	0.022 (6)*
C1	0.7041 (3)	0.5813 (2)	0.89963 (6)	0.0142 (4)
C2	0.4082 (3)	0.5509 (2)	0.95689 (6)	0.0139 (4)
C3	0.3638 (3)	0.3787 (2)	0.92952 (6)	0.0139 (4)
H3	0.2758	0.4047	0.8999	0.017*
C4	0.2637 (3)	0.2364 (2)	0.96165 (7)	0.0171 (4)
H4A	0.1152	0.2510	0.9620	0.021*
H4B	0.3145	0.2403	0.9966	0.021*
C5	0.3244 (3)	0.0629 (2)	0.93578 (7)	0.0186 (4)
H5A	0.2315	0.0353	0.9077	0.022*
H5B	0.3229	−0.0375	0.9598	0.022*
C6	0.5388 (3)	0.0969 (2)	0.91632 (7)	0.0176 (4)
H6A	0.6410	0.0516	0.9402	0.021*
H6B	0.5599	0.0396	0.8833	0.021*
C7	0.7207 (3)	0.3763 (2)	0.90010 (6)	0.0138 (4)
C8	0.9118 (3)	0.6643 (3)	0.90812 (7)	0.0184 (4)
H8A	0.9663	0.6234	0.9403	0.028*
H8B	0.8994	0.7943	0.9085	0.028*
H8C	1.0029	0.6285	0.8810	0.028*
C9	0.6166 (3)	0.6385 (2)	0.84944 (6)	0.0135 (4)
C10	0.4372 (3)	0.7218 (2)	0.84129 (7)	0.0160 (4)
H10	0.3406	0.7490	0.8665	0.019*
C11	0.5846 (3)	0.7053 (2)	0.76602 (7)	0.0165 (4)

C12	0.6367 (3)	0.7248 (3)	0.71558 (7)	0.0208 (4)
H12	0.5487	0.7822	0.6925	0.025*
C13	0.8198 (3)	0.6580 (3)	0.70045 (7)	0.0212 (4)
H13	0.8605	0.6721	0.6665	0.025*
C14	0.9483 (3)	0.5691 (3)	0.73413 (7)	0.0208 (4)
H14	1.0720	0.5208	0.7223	0.025*
C15	0.8978 (3)	0.5507 (2)	0.78411 (6)	0.0164 (4)
H15	0.9853	0.4900	0.8066	0.020*
C16	0.7148 (3)	0.6233 (2)	0.80118 (7)	0.0144 (4)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0186 (7)	0.0201 (7)	0.0152 (6)	0.0020 (6)	0.0040 (6)	−0.0023 (5)
O2	0.0171 (7)	0.0214 (7)	0.0183 (7)	0.0044 (6)	0.0020 (6)	0.0003 (6)
N1	0.0177 (8)	0.0140 (7)	0.0130 (8)	−0.0004 (7)	0.0004 (6)	−0.0043 (6)
N2	0.0151 (8)	0.0130 (7)	0.0145 (8)	0.0029 (7)	0.0009 (6)	−0.0004 (6)
N3	0.0180 (9)	0.0177 (8)	0.0183 (9)	0.0042 (7)	−0.0035 (7)	0.0019 (7)
C1	0.0133 (9)	0.0163 (9)	0.0131 (9)	−0.0003 (8)	0.0012 (7)	−0.0009 (8)
C2	0.0156 (9)	0.0146 (9)	0.0116 (9)	0.0037 (8)	−0.0041 (8)	0.0009 (7)
C3	0.0132 (9)	0.0165 (9)	0.0122 (9)	0.0005 (8)	−0.0004 (7)	−0.0018 (7)
C4	0.0151 (10)	0.0183 (9)	0.0178 (10)	−0.0001 (8)	−0.0015 (7)	0.0010 (8)
C5	0.0218 (11)	0.0156 (9)	0.0183 (10)	−0.0022 (9)	−0.0020 (8)	0.0012 (8)
C6	0.0229 (10)	0.0120 (9)	0.0178 (10)	0.0012 (8)	−0.0012 (8)	−0.0012 (8)
C7	0.0169 (9)	0.0173 (9)	0.0072 (9)	0.0022 (8)	−0.0002 (7)	0.0000 (7)
C8	0.0154 (10)	0.0209 (10)	0.0188 (10)	−0.0008 (9)	−0.0002 (8)	−0.0022 (8)
C9	0.0151 (9)	0.0107 (8)	0.0147 (9)	−0.0033 (8)	−0.0006 (7)	−0.0004 (7)
C10	0.0179 (10)	0.0139 (9)	0.0161 (10)	−0.0031 (8)	0.0004 (7)	−0.0009 (7)
C11	0.0206 (10)	0.0119 (9)	0.0168 (9)	−0.0042 (8)	−0.0008 (8)	−0.0007 (8)
C12	0.0271 (11)	0.0187 (10)	0.0166 (10)	−0.0061 (9)	−0.0049 (8)	0.0024 (8)
C13	0.0288 (11)	0.0197 (10)	0.0152 (10)	−0.0078 (9)	0.0041 (8)	−0.0004 (8)
C14	0.0198 (10)	0.0214 (10)	0.0211 (10)	−0.0053 (9)	0.0040 (8)	−0.0040 (8)
C15	0.0173 (10)	0.0150 (9)	0.0169 (9)	−0.0013 (8)	0.0008 (8)	−0.0005 (7)
C16	0.0174 (9)	0.0112 (8)	0.0147 (9)	−0.0048 (8)	−0.0006 (8)	0.0001 (7)

Geometric parameters (Å, º)

O1—C2	1.228 (2)	C5—H5A	0.9900
O2—C7	1.226 (2)	C5—H5B	0.9900
N1—C2	1.340 (3)	C6—H6A	0.9900
N1—C1	1.472 (2)	C6—H6B	0.9900
N1—H1N	0.90 (2)	C8—H8A	0.9800
N2—C7	1.338 (2)	C8—H8B	0.9800
N2—C3	1.465 (2)	C8—H8C	0.9800
N2—C6	1.474 (2)	C9—C10	1.361 (3)
N3—C11	1.366 (2)	C9—C16	1.445 (2)
N3—C10	1.372 (2)	C10—H10	0.9500
N3—H3N	0.87 (2)	C11—C12	1.395 (3)
C1—C9	1.519 (2)	C11—C16	1.415 (3)
C1—C8	1.528 (3)	C12—C13	1.373 (3)
C1—C7	1.544 (3)	C12—H12	0.9500
C2—C3	1.514 (2)	C13—C14	1.406 (3)

C3—C4	1.522 (3)	C13—H13	0.9500
C3—H3	1.0000	C14—C15	1.380 (3)
C4—C5	1.528 (3)	C14—H14	0.9500
C4—H4A	0.9900	C15—C16	1.405 (3)
C4—H4B	0.9900	C15—H15	0.9500
C5—C6	1.533 (3)		

C2—N1—C1	124.90 (16)	C5—C6—H6A	111.0
C2—N1—H1N	120.1 (14)	N2—C6—H6B	111.0
C1—N1—H1N	114.7 (14)	C5—C6—H6B	111.0
C7—N2—C3	125.26 (15)	H6A—C6—H6B	109.0
C7—N2—C6	121.93 (15)	O2—C7—N2	123.46 (16)
C3—N2—C6	112.23 (15)	O2—C7—C1	122.12 (17)
C11—N3—C10	109.29 (16)	N2—C7—C1	114.39 (16)
C11—N3—H3N	126.7 (13)	C1—C8—H8A	109.5
C10—N3—H3N	123.9 (13)	C1—C8—H8B	109.5
N1—C1—C9	111.67 (15)	H8A—C8—H8B	109.5
N1—C1—C8	107.20 (14)	C1—C8—H8C	109.5
C9—C1—C8	111.00 (15)	H8A—C8—H8C	109.5
N1—C1—C7	108.50 (15)	H8B—C8—H8C	109.5
C9—C1—C7	108.44 (14)	C10—C9—C16	106.70 (15)
C8—C1—C7	110.01 (15)	C10—C9—C1	127.15 (16)
O1—C2—N1	123.30 (17)	C16—C9—C1	126.07 (16)
O1—C2—C3	121.46 (17)	C9—C10—N3	109.96 (16)
N1—C2—C3	115.24 (16)	C9—C10—H10	125.0
N2—C3—C2	111.63 (15)	N3—C10—H10	125.0
N2—C3—C4	103.37 (14)	N3—C11—C12	130.02 (18)
C2—C3—C4	114.47 (15)	N3—C11—C16	107.74 (16)
N2—C3—H3	109.1	C12—C11—C16	122.20 (18)
C2—C3—H3	109.1	C13—C12—C11	117.56 (18)
C4—C3—H3	109.1	C13—C12—H12	121.2
C3—C4—C5	103.38 (15)	C11—C12—H12	121.2
C3—C4—H4A	111.1	C12—C13—C14	121.43 (18)
C5—C4—H4A	111.1	C12—C13—H13	119.3
C3—C4—H4B	111.1	C14—C13—H13	119.3
C5—C4—H4B	111.1	C15—C14—C13	121.09 (19)
H4A—C4—H4B	109.1	C15—C14—H14	119.5
C4—C5—C6	104.70 (16)	C13—C14—H14	119.5
C4—C5—H5A	110.8	C14—C15—C16	118.88 (17)
C6—C5—H5A	110.8	C14—C15—H15	120.6
C4—C5—H5B	110.8	C16—C15—H15	120.6
C6—C5—H5B	110.8	C15—C16—C11	118.73 (16)
H5A—C5—H5B	108.9	C15—C16—C9	134.99 (17)
N2—C6—C5	103.62 (15)	C11—C16—C9	106.28 (16)
N2—C6—H6A	111.0		

C2—N1—C1—C9	80.6 (2)	C8—C1—C7—N2	155.74 (15)
C2—N1—C1—C8	−157.65 (16)	N1—C1—C9—C10	−3.5 (3)
C2—N1—C1—C7	−38.9 (2)	C8—C1—C9—C10	−123.1 (2)
C1—N1—C2—O1	−176.39 (16)	C7—C1—C9—C10	116.0 (2)
C1—N1—C2—C3	4.0 (2)	N1—C1—C9—C16	172.72 (16)
C7—N2—C3—C2	−28.7 (2)	C8—C1—C9—C16	53.2 (2)

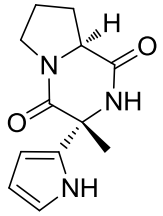
C6—N2—C3—C2	142.67 (15)	C7—C1—C9—C16	−67.8 (2)
C7—N2—C3—C4	−152.19 (16)	C16—C9—C10—N3	−0.3 (2)
C6—N2—C3—C4	19.15 (19)	C1—C9—C10—N3	176.54 (16)
O1—C2—C3—N2	−149.71 (16)	C11—N3—C10—C9	−0.9 (2)
N1—C2—C3—N2	29.9 (2)	C10—N3—C11—C12	−176.1 (2)
O1—C2—C3—C4	−32.7 (2)	C10—N3—C11—C16	1.7 (2)
N1—C2—C3—C4	146.86 (16)	N3—C11—C12—C13	178.73 (18)
N2—C3—C4—C5	−32.86 (18)	C16—C11—C12—C13	1.2 (3)
C2—C3—C4—C5	−154.49 (16)	C11—C12—C13—C14	1.6 (3)
C3—C4—C5—C6	35.14 (18)	C12—C13—C14—C15	−2.1 (3)
C7—N2—C6—C5	174.32 (15)	C13—C14—C15—C16	−0.3 (3)
C3—N2—C6—C5	2.6 (2)	C14—C15—C16—C11	2.9 (3)
C4—C5—C6—N2	−23.41 (18)	C14—C15—C16—C9	−176.58 (19)
C3—N2—C7—O2	174.92 (16)	N3—C11—C16—C15	178.50 (16)
C6—N2—C7—O2	4.4 (3)	C12—C11—C16—C15	−3.5 (3)
C3—N2—C7—C1	−7.1 (2)	N3—C11—C16—C9	−1.87 (19)
C6—N2—C7—C1	−177.63 (15)	C12—C11—C16—C9	176.15 (17)
N1—C1—C7—O2	−143.21 (16)	C10—C9—C16—C15	−179.14 (19)
C9—C1—C7—O2	95.3 (2)	C1—C9—C16—C15	4.0 (3)
C8—C1—C7—O2	−26.2 (2)	C10—C9—C16—C11	1.31 (19)
N1—C1—C7—N2	38.8 (2)	C1—C9—C16—C11	−175.55 (16)
C9—C1—C7—N2	−82.69 (18)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1^{i}	0.90 (2)	2.16 (2)	3.031 (2)	163.5 (19)

Symmetry code: (i) *x*+1/2, −*y*+3/2, −*z*+2.

Appendix 2: Crystallographic data for (2.55)



(**2.55**)

Data obtained at School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

Refinement

The structure was solved by the direct methods. All non-H atoms were refined anisotropically. H atoms were included in calculated positions, except those bonded to the N atoms, which were found by difference Fourier techniques and refined isotropically.

Experimental:

Crystal data

$C_{12}H_{15}N_3O_2$	Z = 6
M_r = 233.27	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hexagonal, $P6_5$	μ = 0.09 mm^{-1}
a = 9.0807 (10) Å	T = 100 K
c = 24.309 (5) Å	0.50 × 0.20 × 0.20 mm
V = 1735.9 (5) $Å^3$	

Data collection

CCD area detector diffractometer	1176 reflections with $I > 2\sigma(I)$
5932 measured reflections	R_{int} = 0.055
1225 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.035	1 restraint
$wR(F^2)$ = 0.086	H atoms treated by a mixture of independent and constrained refinement
S = 1.09	$\Delta\rho_{max}$ = 0.25 e $Å^{-3}$
1225 reflections	$\Delta\rho_{min}$ = −0.20 e $Å^{-3}$
163 parameters	

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*N*···O1^{I}	0.85 (3)	2.17 (3)	2.896 (3)	143 (3)

N1—H1*N*···O2^{ii}	0.86 (3)	1.98 (3)	2.837 (3)	170 (3)

Data collection: Bruker *SMART*; cell refinement: Bruker *SMART*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

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Supplementary materials

Crystal data

$C_{12}H_{15}N_3O_2$	D_x = 1.339 Mg m^{-3}
M_r = 233.27	Mo *K*α radiation, λ = 0.71073 Å
Hexagonal, $P6_5$	Cell parameters from 743 reflections
a = 9.0807 (10) Å	θ = 2.6–25.4°
c = 24.309 (5) Å	μ = 0.09 mm^{-1}
V = 1735.9 (5) Å^3	*T* = 100 K
Z = 6	Rod, Colourless
F(000) = 744	0.50 × 0.20 × 0.20 mm

Data collection

CCD area detector diffractometer	1176 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.055
graphite	θ_{max} = 26.5°, θ_{min} = 2.6°
phi and ω scans	*h* = −8→11
5932 measured reflections	*k* = −9→10
1225 independent reflections	*l* = −29→30

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location:

	Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.035$	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2) = 0.086$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.09$	$w = 1/[\sigma^2(F_o^2) + (0.0538P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
1225 reflections	$(\Delta/\sigma)_{max} = 0.001$
163 parameters	$\Delta\rho_{max} = 0.25$ e Å^{-3}
1 restraint	$\Delta\rho_{min} = -0.20$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.6964 (2)	0.2577 (2)	0.81311 (6)	0.0217 (4)
O2	0.4726 (2)	0.0378 (2)	1.01420 (7)	0.0218 (4)
N1	0.5889 (3)	0.2944 (3)	0.89273 (7)	0.0164 (4)
N2	0.6488 (3)	0.0626 (2)	0.94511 (8)	0.0155 (4)
N3	0.6937 (3)	0.4417 (3)	1.03856 (8)	0.0190 (5)
C1	0.5577 (3)	0.2733 (3)	0.95235 (9)	0.0156 (5)
C2	0.6725 (3)	0.2358 (3)	0.86337 (9)	0.0148 (5)
C3	0.7447 (3)	0.1434 (3)	0.89480 (8)	0.0153 (5)
H3	0.8653	0.2259	0.9048	0.018*
C4	0.7386 (3)	−0.0061 (3)	0.86378 (10)	0.0221 (6)
H4A	0.8358	0.0331	0.8381	0.027*
H4B	0.6312	−0.0702	0.8429	0.027*
C5	0.7497 (4)	−0.1140 (4)	0.91022 (10)	0.0248 (6)
H5A	0.7024	−0.2336	0.8984	0.030*
H5B	0.8690	−0.0687	0.9220	0.030*
C6	0.6435 (3)	−0.1006 (3)	0.95650 (9)	0.0183 (5)
H6A	0.5253	−0.1971	0.9554	0.022*
H6B	0.6936	−0.0981	0.9929	0.022*
C7	0.5557 (3)	0.1122 (3)	0.97286 (9)	0.0166 (5)
C8	0.3842 (3)	0.2566 (3)	0.96375 (10)	0.0204 (5)
H8A	0.3864	0.3614	0.9526	0.031*
H8B	0.3587	0.2372	1.0031	0.031*
H8C	0.2964	0.1605	0.9428	0.031*
C9	0.6978 (3)	0.4251 (3)	0.98236 (9)	0.0155 (5)
C10	0.8394 (3)	0.5654 (3)	0.96276 (10)	0.0181 (5)
H10	0.8749	0.5878	0.9254	0.022*
C11	0.9239 (3)	0.6716 (3)	1.00865 (10)	0.0219 (5)

H11	1.0257	0.7787	1.0077	0.026*
C12	0.8311 (3)	0.5908 (3)	1.05449 (10)	0.0215 (5)
H12	0.8581	0.6318	1.0912	0.026*
H3N	0.622 (4)	0.368 (4)	1.0602 (13)	0.024 (8)*
H1N	0.552 (4)	0.354 (4)	0.8763 (12)	0.024 (8)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0284 (10)	0.0291 (10)	0.0088 (8)	0.0151 (8)	0.0014 (7)	0.0023 (7)
O2	0.0320 (10)	0.0210 (9)	0.0137 (8)	0.0142 (8)	0.0075 (7)	0.0043 (7)
N1	0.0224 (11)	0.0196 (10)	0.0093 (9)	0.0121 (9)	−0.0009 (8)	0.0024 (8)
N2	0.0199 (10)	0.0172 (10)	0.0097 (9)	0.0094 (9)	0.0006 (7)	0.0024 (7)
N3	0.0229 (11)	0.0239 (11)	0.0111 (10)	0.0124 (10)	0.0031 (8)	0.0025 (8)
C1	0.0200 (12)	0.0200 (12)	0.0094 (10)	0.0120 (10)	0.0026 (8)	0.0021 (8)
C2	0.0132 (11)	0.0141 (11)	0.0124 (11)	0.0033 (9)	−0.0017 (9)	0.0009 (8)
C3	0.0162 (11)	0.0193 (12)	0.0087 (10)	0.0075 (10)	−0.0004 (9)	0.0012 (9)
C4	0.0316 (14)	0.0263 (14)	0.0135 (11)	0.0182 (12)	0.0053 (10)	0.0013 (9)
C5	0.0337 (15)	0.0267 (14)	0.0208 (13)	0.0203 (12)	0.0023 (10)	0.0008 (10)
C6	0.0270 (13)	0.0177 (12)	0.0130 (11)	0.0131 (11)	−0.0009 (9)	−0.0008 (9)
C7	0.0210 (12)	0.0157 (11)	0.0099 (10)	0.0069 (10)	−0.0024 (9)	−0.0019 (9)
C8	0.0209 (12)	0.0261 (13)	0.0164 (12)	0.0135 (11)	0.0018 (9)	0.0013 (10)
C9	0.0228 (13)	0.0183 (12)	0.0099 (10)	0.0136 (10)	0.0008 (9)	−0.0001 (8)
C10	0.0207 (12)	0.0199 (12)	0.0158 (11)	0.0116 (11)	0.0016 (9)	0.0028 (9)
C11	0.0213 (12)	0.0218 (13)	0.0208 (12)	0.0094 (10)	−0.0026 (10)	−0.0018 (10)
C12	0.0275 (13)	0.0264 (13)	0.0137 (11)	0.0159 (11)	−0.0048 (10)	−0.0057 (10)

Geometric parameters (Å, º)

O1—C2	1.239 (3)	C4—C5	1.531 (3)
O2—C7	1.235 (3)	C4—H4A	0.9900
N1—C2	1.331 (3)	C4—H4B	0.9900
N1—C1	1.471 (3)	C5—C6	1.526 (3)
N1—H1N	0.86 (3)	C5—H5A	0.9900
N2—C7	1.324 (3)	C5—H5B	0.9900
N2—C3	1.468 (3)	C6—H6A	0.9900
N2—C6	1.484 (3)	C6—H6B	0.9900
N3—C12	1.360 (3)	C8—H8A	0.9800
N3—C9	1.377 (3)	C8—H8B	0.9800
N3—H3N	0.85 (3)	C8—H8C	0.9800
C1—C9	1.516 (3)	C9—C10	1.366 (3)
C1—C8	1.531 (3)	C10—C11	1.422 (3)
C1—C7	1.537 (3)	C10—H10	0.9500
C2—C3	1.507 (3)	C11—C12	1.368 (4)
C3—C4	1.529 (3)	C11—H11	0.9500
C3—H3	1.0000	C12—H12	0.9500

C2—N1—C1	126.0 (2)	C4—C5—H5A	110.9
C2—N1—H1N	118.7 (19)	C6—C5—H5B	110.9
C1—N1—H1N	115 (2)	C4—C5—H5B	110.9
C7—N2—C3	125.1 (2)	H5A—C5—H5B	108.9
C7—N2—C6	122.47 (19)	N2—C6—C5	103.65 (19)

C3—N2—C6	111.69 (18)	N2—C6—H6A	111.0
C12—N3—C9	109.3 (2)	C5—C6—H6A	111.0
C12—N3—H3N	125 (2)	N2—C6—H6B	111.0
C9—N3—H3N	126 (2)	C5—C6—H6B	111.0
N1—C1—C9	109.67 (18)	H6A—C6—H6B	109.0
N1—C1—C8	108.25 (18)	O2—C7—N2	123.2 (2)
C9—C1—C8	110.94 (19)	O2—C7—C1	119.8 (2)
N1—C1—C7	110.68 (19)	N2—C7—C1	116.93 (19)
C9—C1—C7	108.33 (18)	C1—C8—H8A	109.5
C8—C1—C7	108.98 (19)	C1—C8—H8B	109.5
O1—C2—N1	123.6 (2)	H8A—C8—H8B	109.5
O1—C2—C3	119.9 (2)	C1—C8—H8C	109.5
N1—C2—C3	116.40 (19)	H8A—C8—H8C	109.5
N2—C3—C2	112.73 (19)	H8B—C8—H8C	109.5
N2—C3—C4	102.61 (19)	C10—C9—N3	108.0 (2)
C2—C3—C4	114.34 (19)	C10—C9—C1	130.6 (2)
N2—C3—H3	109.0	N3—C9—C1	121.4 (2)
C2—C3—H3	109.0	C9—C10—C11	107.2 (2)
C4—C3—H3	109.0	C9—C10—H10	126.4
C3—C4—C5	102.71 (19)	C11—C10—H10	126.4
C3—C4—H4A	111.2	C12—C11—C10	107.3 (2)
C5—C4—H4A	111.2	C12—C11—H11	126.4
C3—C4—H4B	111.2	C10—C11—H11	126.4
C5—C4—H4B	111.2	N3—C12—C11	108.3 (2)
H4A—C4—H4B	109.1	N3—C12—H12	125.8
C6—C5—C4	104.2 (2)	C11—C12—H12	125.8
C6—C5—H5A	110.9		

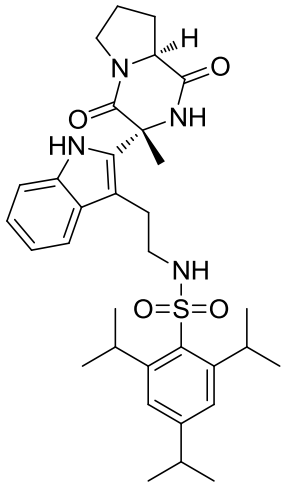
C2—N1—C1—C9	92.7 (3)	C3—N2—C7—C1	−3.8 (3)
C2—N1—C1—C8	−146.1 (2)	C6—N2—C7—C1	−173.0 (2)
C2—N1—C1—C7	−26.7 (3)	N1—C1—C7—O2	−152.9 (2)
C1—N1—C2—O1	−179.6 (2)	C9—C1—C7—O2	86.8 (3)
C1—N1—C2—C3	−1.5 (3)	C8—C1—C7—O2	−33.9 (3)
C7—N2—C3—C2	−25.1 (3)	N1—C1—C7—N2	28.7 (3)
C6—N2—C3—C2	145.0 (2)	C9—C1—C7—N2	−91.6 (2)
C7—N2—C3—C4	−148.6 (2)	C8—C1—C7—N2	147.6 (2)
C6—N2—C3—C4	21.6 (2)	C12—N3—C9—C10	0.0 (3)
O1—C2—C3—N2	−154.5 (2)	C12—N3—C9—C1	−178.2 (2)
N1—C2—C3—N2	27.4 (3)	N1—C1—C9—C10	−1.5 (3)
O1—C2—C3—C4	−37.8 (3)	C8—C1—C9—C10	−121.0 (3)
N1—C2—C3—C4	144.1 (2)	C7—C1—C9—C10	119.4 (3)
N2—C3—C4—C5	−36.0 (2)	N1—C1—C9—N3	176.2 (2)
C2—C3—C4—C5	−158.4 (2)	C8—C1—C9—N3	56.7 (3)
C3—C4—C5—C6	38.0 (3)	C7—C1—C9—N3	−62.9 (3)
C7—N2—C6—C5	172.4 (2)	N3—C9—C10—C11	−0.4 (3)
C3—N2—C6—C5	2.0 (2)	C1—C9—C10—C11	177.6 (2)
C4—C5—C6—N2	−24.8 (3)	C9—C10—C11—C12	0.6 (3)
C3—N2—C7—O2	177.8 (2)	C9—N3—C12—C11	0.4 (3)
C6—N2—C7—O2	8.6 (3)	C10—C11—C12—N3	−0.6 (3)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*N*···O1^{i}	0.85 (3)	2.17 (3)	2.896 (3)	143 (3)
N1—H1*N*···O2^{ii}	0.86 (3)	1.98 (3)	2.837 (3)	170 (3)

Symmetry codes: (i) −*x*+*y*+1, −*x*+1, *z*+1/3; (ii) *x*−*y*, *x*, *z*−1/6.

Appendix 3: Crystallographic data for (2.62)



(**2.62**)

Data obtained at School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

Refinement

The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. H atoms were included in calculated positions with C—H lengths of 0.95(CH), 0.99(CH_2) & 0.98(CH_3)Å; U_{iso}(H) values were fixed at 1.2U_{eq}(C) except for CH_3 where it was 1.5U_{eq}(C).

Experimental:

Crystal data

$C_{33}H_{44}N_4O_4S$	V = 7171.3 (15) Å^3
M_r = 592.78	Z = 8
Monoclinic, $C2$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 34.745 (4) Å	μ = 0.13 mm^{-1}
b = 10.7638 (12) Å	T = 100 K
c = 25.643 (3) Å	0.30 × 0.25 × 0.10 mm
β = 131.602 (5)°	

Data collection

CCD area detector diffractometer	6382 reflections with $I > 2\sigma(I)$
28840 measured reflections	R_{int} = 0.097
14299 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.101	H-atom parameters constrained
$wR(F^2)$ = 0.299	$\Delta\rho_{max}$ = 1.40 e Å^{-3}
S = 0.95	$\Delta\rho_{min}$ = −0.48 e Å^{-3}

14299 reflections	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
771 parameters	Flack parameter: −0.05 (17)
22 restraints	

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5—H5*A*···O3^{i}	0.88	1.95	2.819 (9)	169
N1—H1···O7^{ii}	0.88	1.98	2.850 (8)	171
N7—H7*A*···O6^{III}	0.88	2.21	2.849 (10)	129
N6—H6···O6^{iii}	0.88	2.41	3.195 (12)	150
N3—H3*A*···O1^{iv}	0.88	2.35	3.002 (8)	131
N2—H2···O1^{iv}	0.88	2.17	3.010 (8)	160

Data collection: Bruker *SMART*; cell refinement: Bruker *SMART*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

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Supplementary materials

Crystal data

$C_{33}H_{44}N_4O_4S$	*F*(000) = 2544
M_r = 592.78	D_x = 1.098 Mg m^{-3}
Monoclinic, *C*2	Mo *K*α radiation, λ = 0.71073 Å
a = 34.745 (4) Å	Cell parameters from 1493 reflections
b = 10.7638 (12) Å	θ = 2.3–17.8°
c = 25.643 (3) Å	μ = 0.13 mm^{-1}
β = 131.602 (5)°	*T* = 100 K
V = 7171.3 (15) Å^3	Plate, White
Z = 8	0.30 × 0.25 × 0.10 mm

Data collection

CCD area detector diffractometer	6382 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.097$
graphite	$\theta_{max} = 26.4°$, $\theta_{min} = 1.2°$
phi and ω scans	$h = -43 \rightarrow 43$
28840 measured reflections	$k = -13 \rightarrow 13$
14299 independent reflections	$l = -31 \rightarrow 32$

Refinement

Refinement on F^2	Secondary atom site location: Difference Fourier map
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.101$	H-atom parameters constrained
$wR(F^2) = 0.299$	$w = 1/[\sigma^2(F_o^2) + (0.1303P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 0.95$	$(\Delta/\sigma)_{max} = 1.966$
14299 reflections	$\Delta\rho_{max} = 1.40$ e Å^{-3}
771 parameters	$\Delta\rho_{min} = -0.48$ e Å^{-3}
22 restraints	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: Structure-invariant direct methods	Flack parameter: −0.05 (17)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C19	0.7773 (3)	0.6722 (7)	0.3568 (4)	0.0195 (17)
C20	0.8129 (3)	0.7554 (8)	0.3683 (4)	0.0258 (19)
H20	0.8088	0.8422	0.3700	0.031*
C21	0.8538 (4)	0.7115 (9)	0.3773 (5)	0.040 (2)
H21	0.8782	0.7681	0.3852	0.047*
C22	0.8600 (4)	0.5833 (9)	0.3748 (5)	0.047 (3)
H22	0.8881	0.5544	0.3797	0.057*
C23	0.8254 (4)	0.4971 (9)	0.3652 (6)	0.044 (3)
H23	0.8304	0.4103	0.3652	0.052*
C24	0.7845 (3)	0.5424 (8)	0.3559 (4)	0.0257 (19)
C25	0.7114 (3)	0.5681 (7)	0.3364 (4)	0.0180 (17)
C26	0.6638 (3)	0.5194 (7)	0.3191 (4)	0.0181 (17)

C27	0.6361 (3)	0.6141 (8)	0.3292 (4)	0.0224 (17)
C28	0.6311 (3)	0.6954 (8)	0.4159 (4)	0.031 (2)
H28A	0.5993	0.6540	0.3995	0.037*
H28B	0.6228	0.7816	0.3978	0.037*
C29	0.6727 (3)	0.6935 (7)	0.4953 (4)	0.0262 (19)
H29A	0.6574	0.6975	0.5168	0.031*
H29B	0.6969	0.7637	0.5127	0.031*
C30	0.6998 (3)	0.5687 (8)	0.5108 (4)	0.028 (2)
H30A	0.6802	0.4999	0.5094	0.033*
H30B	0.7350	0.5699	0.5572	0.033*
C31	0.7015 (3)	0.5540 (7)	0.4523 (4)	0.0236 (18)
H31	0.7329	0.5967	0.4670	0.028*
C32	0.7005 (3)	0.4242 (7)	0.4309 (4)	0.0212 (18)
C33	0.6255 (3)	0.4763 (9)	0.2426 (4)	0.036 (2)
H33A	0.6415	0.4114	0.2356	0.054*
H33B	0.6162	0.5469	0.2119	0.054*
H33C	0.5945	0.4431	0.2314	0.054*
C52	0.9233 (4)	0.5840 (8)	0.2304 (6)	0.047 (3)
C53	0.8869 (6)	0.5048 (12)	0.2228 (9)	0.100 (6)
H53	0.8905	0.4170	0.2243	0.119*
C54	0.8465 (5)	0.5574 (13)	0.2133 (9)	0.090 (5)
H54	0.8209	0.5054	0.2052	0.108*
C55	0.8427 (5)	0.6836 (15)	0.2156 (7)	0.081 (4)
H55	0.8167	0.7169	0.2142	0.097*
C56	0.8762 (5)	0.7646 (13)	0.2198 (8)	0.098 (6)
H56	0.8719	0.8522	0.2170	0.118*
C57	0.9171 (3)	0.7076 (9)	0.2286 (5)	0.038 (2)
C58	0.9868 (3)	0.6738 (7)	0.2447 (4)	0.0200 (17)
C59	1.0319 (3)	0.7160 (7)	0.2518 (4)	0.028 (2)
C60	1.0764 (3)	0.6201 (9)	0.2879 (4)	0.0297 (19)
C61	1.1526 (3)	0.5409 (9)	0.4074 (5)	0.036 (2)
H61A	1.1493	0.4555	0.3905	0.043*
H61B	1.1817	0.5831	0.4159	0.043*
C62	1.1596 (3)	0.5401 (8)	0.4713 (5)	0.035 (2)
H62A	1.1962	0.5299	0.5139	0.043*
H62B	1.1391	0.4732	0.4695	0.043*
C63	1.1392 (3)	0.6707 (8)	0.4685 (4)	0.030 (2)
H63A	1.1306	0.6737	0.4984	0.037*
H63B	1.1651	0.7356	0.4841	0.037*
C64	1.0911 (3)	0.6889 (8)	0.3922 (4)	0.028 (2)
H64	1.0604	0.6543	0.3830	0.034*
C65	1.0808 (3)	0.8222 (8)	0.3663 (4)	0.0269 (19)
C66	1.0133 (3)	0.7469 (8)	0.1803 (4)	0.030 (2)
H66A	0.9891	0.8165	0.1600	0.045*
H66B	0.9961	0.6742	0.1497	0.045*
H66C	1.0428	0.7698	0.1850	0.045*
N2	0.7437 (2)	0.4839 (6)	0.3426 (3)	0.0230 (15)
H2	0.7389	0.4029	0.3387	0.028*
N3	0.6774 (2)	0.4117 (6)	0.3644 (3)	0.0216 (15)
H3A	0.6698	0.3365	0.3465	0.026*
N4	0.6555 (2)	0.6246 (6)	0.3941 (3)	0.0219 (14)
N6	0.9560 (3)	0.7613 (7)	0.2378 (4)	0.042 (2)

H6	0.9607	0.8420	0.2391	0.051*
N7	1.0550 (3)	0.8298 (6)	0.2971 (4)	0.0301 (17)
H7A	1.0519	0.9022	0.2786	0.036*
N8	1.1031 (2)	0.6132 (7)	0.3562 (3)	0.0296 (16)
O3	0.5983 (2)	0.6739 (6)	0.2801 (3)	0.0355 (15)
O4	0.7219 (2)	0.3398 (5)	0.4723 (3)	0.0314 (14)
O7	1.0852 (2)	0.5622 (5)	0.2554 (3)	0.0312 (14)
O8	1.0928 (2)	0.9119 (5)	0.4026 (3)	0.0363 (15)
C1	0.6991 (3)	1.1304 (8)	0.2043 (4)	0.0261 (19)
C2	0.6471 (3)	1.1362 (7)	0.1418 (4)	0.0287 (19)
C3	0.6378 (3)	1.1386 (8)	0.0791 (4)	0.033 (2)
H3	0.6032	1.1399	0.0360	0.040*
C4	0.6768 (4)	1.1392 (10)	0.0783 (5)	0.045 (2)
C5	0.7272 (4)	1.1423 (9)	0.1406 (5)	0.044 (2)
H5	0.7540	1.1468	0.1395	0.052*
C6	0.7401 (3)	1.1391 (8)	0.2053 (4)	0.032 (2)
C7	0.6002 (3)	1.1466 (8)	0.1349 (4)	0.035 (2)
H7	0.6127	1.1600	0.1826	0.042*
C8	0.5671 (3)	1.0304 (8)	0.1048 (5)	0.037 (2)
H8A	0.5549	1.0145	0.0582	0.056*
H8B	0.5376	1.0422	0.1015	0.056*
H8C	0.5876	0.9594	0.1352	0.056*
C9	0.5680 (4)	1.2591 (9)	0.0903 (5)	0.040 (2)
H9A	0.5902	1.3324	0.1077	0.060*
H9B	0.5414	1.2737	0.0928	0.060*
H9C	0.5516	1.2435	0.0418	0.060*
C10	0.6635 (4)	1.1404 (13)	0.0085 (5)	0.073 (4)
H10	0.6968	1.1370	0.0188	0.087*
C11	0.6374 (5)	1.2650 (12)	−0.0291 (6)	0.070 (4)
H11A	0.6368	1.2749	−0.0676	0.105*
H11B	0.6567	1.3336	0.0039	0.105*
H11C	0.6020	1.2653	−0.0476	0.105*
C12	0.6328 (6)	1.0335 (12)	−0.0360 (6)	0.081 (4)
H12A	0.6051	1.0187	−0.0358	0.122*
H12B	0.6549	0.9598	−0.0182	0.122*
H12C	0.6180	1.0506	−0.0838	0.122*
C13	0.7970 (3)	1.1494 (8)	0.2674 (5)	0.039 (2)
H13	0.8013	1.1680	0.3093	0.047*
C14	0.8212 (5)	1.2566 (10)	0.2582 (6)	0.060 (3)
H14A	0.8255	1.2315	0.2255	0.091*
H14B	0.8548	1.2772	0.3034	0.091*
H14C	0.7987	1.3295	0.2397	0.091*
C15	0.8253 (4)	1.0294 (10)	0.2812 (6)	0.055 (3)
H15A	0.8108	0.9620	0.2892	0.083*
H15B	0.8619	1.0394	0.3225	0.083*
H15C	0.8216	1.0092	0.2408	0.083*
S1	0.71209 (7)	1.10994 (17)	0.28479 (10)	0.0201 (4)
O1	0.6993 (2)	1.2256 (5)	0.2999 (3)	0.0275 (14)
O2	0.7639 (2)	1.0636 (5)	0.3355 (3)	0.0268 (13)
N1	0.6735 (2)	1.0097 (6)	0.2728 (3)	0.0234 (16)
H1	0.6462	1.0343	0.2658	0.028*
C16	0.6828 (3)	0.8732 (6)	0.2733 (4)	0.0187 (17)

H16A	0.7033	0.8611	0.2597	0.022*
H16B	0.6493	0.8308	0.2382	0.022*
C17	0.7106 (3)	0.8144 (6)	0.3435 (4)	0.0188 (17)
H17A	0.6867	0.8055	0.3519	0.023*
H17B	0.7395	0.8684	0.3805	0.023*
C18	0.7312 (3)	0.6870 (7)	0.3464 (4)	0.0205 (18)
C34	0.9092 (3)	0.1454 (8)	0.0958 (4)	0.0218 (17)
C35	0.8566 (4)	0.1511 (10)	0.0599 (4)	0.044 (2)
C36	0.8220 (4)	0.1471 (11)	−0.0146 (5)	0.053 (3)
H36	0.7860	0.1453	−0.0407	0.064*
C37	0.8394 (4)	0.1459 (11)	−0.0496 (5)	0.052 (3)
C38	0.8937 (3)	0.1496 (10)	−0.0091 (5)	0.048 (3)
H38	0.9063	0.1585	−0.0324	0.057*
C39	0.9279 (3)	0.1409 (8)	0.0613 (4)	0.035 (2)
C40	0.8308 (3)	0.1472 (12)	0.0899 (5)	0.060 (4)
H40	0.8579	0.1523	0.1419	0.072*
C41	0.7939 (5)	0.2594 (11)	0.0624 (8)	0.090 (5)
H41A	0.8139	0.3365	0.0813	0.135*
H41B	0.7742	0.2512	0.0772	0.135*
H41C	0.7701	0.2614	0.0114	0.135*
C42	0.7992 (7)	0.0267 (11)	0.0694 (10)	0.138 (9)
H42A	0.7784	0.0105	0.0195	0.207*
H42B	0.7765	0.0365	0.0793	0.207*
H42C	0.8226	−0.0432	0.0965	0.207*
C43	0.7995 (4)	0.1469 (14)	−0.1308 (5)	0.083 (5)
H43	0.7666	0.1167	−0.1444	0.099*
C44	0.7887 (5)	0.2872 (12)	−0.1561 (6)	0.091 (5)
H44A	0.8193	0.3221	−0.1454	0.136*
H44B	0.7807	0.3353	−0.1319	0.136*
H44C	0.7595	0.2908	−0.2065	0.136*
C45	0.8110 (8)	0.060 (3)	−0.1612 (7)	0.30 (2)
H45A	0.8199	0.1053	−0.1851	0.452*
H45B	0.7808	0.0075	−0.1949	0.452*
H45C	0.8401	0.0078	−0.1245	0.452*
C46	0.9838 (3)	0.1290 (9)	0.0953 (5)	0.040 (2)
H46	1.0048	0.1142	0.1463	0.048*
C47	1.0032 (5)	0.2483 (10)	0.0866 (7)	0.068 (4)
H47A	0.9872	0.2569	0.0378	0.102*
H47B	1.0407	0.2440	0.1164	0.102*
H47C	0.9942	0.3201	0.1001	0.102*
C48	0.9909 (4)	0.0197 (9)	0.0656 (5)	0.042 (3)
H48A	0.9752	0.0383	0.0176	0.063*
H48B	0.9744	−0.0538	0.0658	0.063*
H48C	1.0277	0.0036	0.0940	0.063*
S2	0.95557 (8)	0.1332 (2)	0.18921 (11)	0.0404 (6)
O5	0.9292 (3)	0.1577 (10)	0.2141 (3)	0.086 (3)
O6	0.9827 (3)	0.0188 (7)	0.2060 (4)	0.071 (3)
N5	0.9968 (3)	0.2380 (8)	0.2169 (6)	0.085 (4)
H5A	1.0293	0.2176	0.2418	0.103*
C49	0.9800 (5)	0.3832 (12)	0.2000 (6)	0.097 (6)
H49A	0.9984	0.4282	0.1886	0.116*
H49B	0.9425	0.3919	0.1608	0.116*

C50	0.9952 (5)	0.4289 (15)	0.2654 (6)	0.131 (9)
H50A	1.0330	0.4365	0.3027	0.157*
H50B	0.9818	0.3752	0.2816	0.157*
C51	0.9675 (4)	0.5626 (9)	0.2400 (7)	0.060 (4)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C19	0.017 (4)	0.016 (4)	0.022 (4)	0.003 (3)	0.012 (3)	0.005 (3)
C20	0.029 (5)	0.023 (4)	0.026 (5)	−0.002 (4)	0.018 (4)	0.001 (4)
C21	0.035 (5)	0.045 (6)	0.039 (6)	−0.009 (5)	0.025 (5)	0.006 (5)
C22	0.029 (5)	0.052 (7)	0.066 (7)	0.018 (5)	0.034 (6)	0.009 (5)
C23	0.042 (6)	0.027 (5)	0.070 (8)	0.006 (5)	0.040 (6)	0.004 (5)
C24	0.020 (4)	0.025 (5)	0.028 (5)	0.006 (4)	0.014 (4)	0.004 (4)
C25	0.019 (4)	0.016 (4)	0.011 (4)	0.002 (3)	0.007 (3)	−0.002 (3)
C26	0.017 (4)	0.018 (4)	0.015 (4)	−0.007 (3)	0.009 (3)	−0.003 (3)
C27	0.015 (4)	0.023 (4)	0.024 (4)	0.004 (4)	0.011 (3)	0.001 (4)
C28	0.037 (5)	0.017 (4)	0.044 (5)	0.001 (4)	0.029 (5)	0.001 (4)
C29	0.037 (5)	0.017 (4)	0.030 (5)	−0.002 (4)	0.025 (4)	−0.005 (4)
C30	0.024 (4)	0.039 (5)	0.021 (4)	−0.007 (4)	0.015 (4)	−0.002 (4)
C31	0.029 (5)	0.018 (4)	0.025 (4)	0.003 (4)	0.018 (4)	0.002 (3)
C32	0.020 (4)	0.019 (4)	0.033 (5)	0.006 (4)	0.021 (4)	0.002 (4)
C33	0.032 (5)	0.045 (6)	0.024 (5)	−0.004 (4)	0.016 (4)	−0.001 (4)
C52	0.048 (6)	0.026 (6)	0.094 (9)	0.010 (4)	0.058 (7)	0.017 (5)
C53	0.101 (11)	0.040 (8)	0.217 (19)	0.024 (7)	0.131 (13)	0.050 (9)
C54	0.083 (10)	0.060 (9)	0.180 (16)	0.022 (8)	0.110 (12)	0.057 (10)
C55	0.052 (8)	0.103 (12)	0.119 (12)	−0.010 (8)	0.070 (9)	−0.014 (9)
C56	0.064 (9)	0.078 (10)	0.155 (15)	−0.015 (8)	0.073 (10)	−0.070 (10)
C57	0.031 (5)	0.049 (6)	0.048 (6)	0.002 (5)	0.032 (5)	−0.013 (5)
C58	0.015 (4)	0.022 (4)	0.020 (4)	0.002 (3)	0.010 (3)	0.001 (3)
C59	0.022 (4)	0.017 (4)	0.035 (5)	−0.001 (3)	0.015 (4)	−0.001 (4)
C60	0.016 (4)	0.038 (5)	0.032 (4)	−0.014 (4)	0.015 (4)	−0.002 (4)
C61	0.023 (5)	0.032 (5)	0.051 (6)	0.011 (4)	0.023 (5)	0.017 (4)
C62	0.020 (5)	0.025 (5)	0.038 (5)	0.002 (4)	0.010 (4)	0.005 (4)
C63	0.031 (5)	0.031 (5)	0.021 (4)	−0.005 (4)	0.014 (4)	0.000 (4)
C64	0.036 (5)	0.028 (5)	0.028 (5)	0.003 (4)	0.024 (4)	0.001 (4)
C65	0.015 (4)	0.031 (5)	0.033 (5)	0.002 (4)	0.015 (4)	0.001 (4)
C66	0.031 (5)	0.033 (5)	0.028 (5)	−0.003 (4)	0.020 (4)	0.001 (4)
N2	0.026 (4)	0.017 (4)	0.023 (4)	0.006 (3)	0.015 (3)	0.005 (3)
N3	0.023 (4)	0.011 (3)	0.031 (4)	−0.006 (3)	0.018 (3)	−0.008 (3)
N4	0.022 (3)	0.015 (3)	0.027 (3)	0.003 (3)	0.016 (3)	−0.004 (3)
N6	0.028 (4)	0.028 (4)	0.065 (6)	−0.002 (4)	0.028 (4)	−0.023 (4)
N7	0.036 (4)	0.021 (4)	0.030 (4)	0.001 (3)	0.020 (4)	0.006 (3)
N8	0.028 (4)	0.021 (4)	0.036 (4)	0.007 (3)	0.020 (3)	0.008 (3)
O3	0.023 (3)	0.044 (4)	0.030 (3)	0.008 (3)	0.014 (3)	0.005 (3)
O4	0.043 (4)	0.023 (3)	0.034 (3)	0.010 (3)	0.027 (3)	0.007 (3)
O7	0.020 (3)	0.038 (4)	0.037 (4)	−0.001 (3)	0.019 (3)	−0.010 (3)
O8	0.038 (4)	0.019 (3)	0.035 (4)	0.002 (3)	0.017 (3)	−0.002 (3)
C1	0.041 (5)	0.028 (5)	0.016 (4)	0.014 (4)	0.022 (4)	0.011 (4)
C2	0.042 (5)	0.012 (4)	0.038 (5)	0.000 (4)	0.029 (4)	−0.004 (4)
C3	0.036 (5)	0.034 (5)	0.022 (4)	0.008 (4)	0.016 (4)	0.007 (4)
C4	0.058 (6)	0.051 (7)	0.035 (5)	0.009 (6)	0.035 (5)	0.003 (5)

C5	0.048 (6)	0.048 (7)	0.053 (6)	0.019 (5)	0.042 (5)	0.010 (5)
C6	0.050 (5)	0.028 (5)	0.035 (5)	0.011 (4)	0.035 (4)	0.008 (4)
C7	0.034 (5)	0.036 (6)	0.022 (4)	0.011 (4)	0.013 (4)	0.006 (4)
C8	0.036 (5)	0.030 (5)	0.036 (5)	0.005 (4)	0.020 (5)	0.000 (4)
C9	0.041 (6)	0.039 (6)	0.038 (6)	0.014 (5)	0.026 (5)	0.009 (5)
C10	0.052 (6)	0.142 (13)	0.042 (6)	0.015 (9)	0.039 (6)	0.008 (8)
C11	0.068 (8)	0.102 (10)	0.035 (6)	−0.010 (7)	0.032 (6)	0.028 (7)
C12	0.115 (12)	0.084 (10)	0.056 (8)	−0.036 (9)	0.061 (9)	−0.025 (7)
C13	0.048 (6)	0.033 (6)	0.053 (6)	0.000 (5)	0.041 (5)	0.003 (5)
C14	0.086 (9)	0.062 (8)	0.073 (8)	−0.005 (7)	0.069 (8)	0.005 (6)
C15	0.038 (6)	0.061 (8)	0.059 (7)	0.008 (6)	0.029 (6)	0.007 (6)
S1	0.0292 (11)	0.0142 (9)	0.0247 (10)	−0.0004 (9)	0.0212 (9)	−0.0007 (8)
O1	0.041 (4)	0.021 (3)	0.033 (3)	−0.009 (3)	0.030 (3)	−0.007 (3)
O2	0.027 (3)	0.024 (3)	0.030 (3)	−0.004 (2)	0.019 (3)	0.002 (2)
N1	0.017 (4)	0.024 (4)	0.026 (4)	0.006 (3)	0.013 (3)	0.005 (3)
C16	0.019 (4)	0.009 (4)	0.020 (4)	0.005 (3)	0.010 (4)	0.004 (3)
C17	0.023 (4)	0.007 (4)	0.031 (4)	−0.003 (3)	0.019 (4)	−0.001 (3)
C18	0.018 (4)	0.023 (4)	0.014 (4)	−0.006 (3)	0.008 (3)	−0.002 (3)
C34	0.014 (4)	0.028 (5)	0.017 (4)	0.012 (3)	0.008 (3)	0.010 (3)
C35	0.046 (6)	0.057 (7)	0.028 (5)	0.006 (5)	0.024 (5)	0.006 (5)
C36	0.031 (5)	0.089 (9)	0.041 (6)	0.003 (6)	0.025 (5)	−0.001 (6)
C37	0.049 (6)	0.074 (8)	0.032 (5)	0.033 (6)	0.026 (5)	0.018 (5)
C38	0.042 (6)	0.067 (8)	0.052 (6)	0.027 (6)	0.039 (5)	0.017 (6)
C39	0.030 (5)	0.029 (5)	0.037 (5)	0.016 (4)	0.018 (4)	0.013 (4)
C40	0.034 (5)	0.122 (11)	0.027 (5)	0.005 (7)	0.022 (4)	0.005 (6)
C41	0.127 (13)	0.061 (9)	0.172 (15)	0.000 (9)	0.137 (13)	−0.011 (9)
C42	0.27 (2)	0.046 (8)	0.30 (3)	0.034 (12)	0.27 (2)	0.036 (12)
C43	0.046 (6)	0.165 (15)	0.035 (6)	0.058 (9)	0.026 (5)	0.020 (8)
C44	0.061 (8)	0.120 (13)	0.058 (8)	−0.001 (8)	0.025 (7)	0.059 (8)
C45	0.19 (2)	0.56 (5)	0.027 (8)	0.24 (3)	0.023 (11)	−0.031 (16)
C46	0.031 (5)	0.053 (6)	0.044 (5)	0.001 (5)	0.029 (4)	−0.003 (5)
C47	0.064 (8)	0.054 (8)	0.111 (11)	−0.003 (6)	0.068 (8)	0.001 (7)
C48	0.034 (5)	0.046 (6)	0.047 (6)	0.020 (5)	0.028 (5)	0.010 (5)
S2	0.0301 (12)	0.0451 (16)	0.0223 (11)	0.0036 (12)	0.0074 (10)	−0.0036 (11)
O5	0.054 (4)	0.171 (10)	0.031 (4)	0.002 (6)	0.028 (4)	−0.016 (5)
O6	0.055 (5)	0.043 (5)	0.051 (5)	0.012 (4)	0.009 (4)	0.014 (4)
N5	0.020 (4)	0.043 (6)	0.122 (9)	0.002 (4)	0.017 (5)	−0.061 (6)
C49	0.059 (8)	0.177 (17)	0.043 (8)	−0.074 (10)	0.029 (7)	−0.042 (9)
C50	0.036 (7)	0.32 (3)	0.039 (8)	0.017 (12)	0.024 (7)	0.034 (12)
C51	0.052 (7)	0.020 (5)	0.134 (11)	0.016 (5)	0.073 (8)	0.020 (6)

Geometric parameters (Å, º)

C19—C20	1.391 (11)	C5—H5	0.9500
C19—C24	1.422 (10)	C6—C13	1.508 (12)
C19—C18	1.446 (10)	C7—C8	1.518 (11)
C20—C21	1.365 (12)	C7—C9	1.526 (11)
C20—H20	0.9500	C7—H7	1.0000
C21—C22	1.405 (13)	C8—H8A	0.9800
C21—H21	0.9500	C8—H8B	0.9800
C22—C23	1.404 (13)	C8—H8C	0.9800
C22—H22	0.9500	C9—H9A	0.9800

C23—C24	1.365 (11)	C9—H9B	0.9800
C23—H23	0.9500	C9—H9C	0.9800
C24—N2	1.374 (10)	C10—C12	1.464 (14)
C25—N2	1.366 (9)	C10—C11	1.546 (15)
C25—C18	1.393 (10)	C10—H10	1.0000
C25—C26	1.495 (10)	C11—H11A	0.9800
C26—N3	1.480 (9)	C11—H11B	0.9800
C26—C27	1.538 (10)	C11—H11C	0.9800
C26—C33	1.539 (10)	C12—H12A	0.9800
C27—O3	1.236 (9)	C12—H12B	0.9800
C27—N4	1.321 (8)	C12—H12C	0.9800
C28—N4	1.499 (9)	C13—C15	1.517 (12)
C28—C29	1.525 (11)	C13—C14	1.536 (12)
C28—H28A	0.9900	C13—H13	1.0000
C28—H28B	0.9900	C14—H14A	0.9800
C29—C30	1.534 (11)	C14—H14B	0.9800
C29—H29A	0.9900	C14—H14C	0.9800
C29—H29B	0.9900	C15—H15A	0.9800
C30—C31	1.547 (10)	C15—H15B	0.9800
C30—H30A	0.9900	C15—H15C	0.9800
C30—H30B	0.9900	S1—O2	1.439 (6)
C31—N4	1.479 (9)	S1—O1	1.458 (5)
C31—C32	1.493 (10)	S1—N1	1.584 (6)
C31—H31	1.0000	N1—C16	1.503 (9)
C32—O4	1.208 (9)	N1—H1	0.8800
C32—N3	1.323 (10)	C16—C17	1.506 (9)
C33—H33A	0.9800	C16—H16A	0.9900
C33—H33B	0.9800	C16—H16B	0.9900
C33—H33C	0.9800	C17—C18	1.527 (10)
C52—C57	1.344 (13)	C17—H17A	0.9900
C52—C51	1.402 (12)	C17—H17B	0.9900
C52—C53	1.427 (14)	C34—C35	1.399 (11)
C53—C54	1.379 (16)	C34—C39	1.406 (11)
C53—H53	0.9500	C34—S2	1.796 (7)
C54—C55	1.369 (17)	C35—C36	1.431 (12)
C54—H54	0.9500	C35—C40	1.520 (12)
C55—C56	1.398 (18)	C36—C37	1.375 (12)
C55—H55	0.9500	C36—H36	0.9500
C56—C57	1.422 (14)	C37—C38	1.427 (12)
C56—H56	0.9500	C37—C43	1.556 (13)
C57—N6	1.340 (11)	C38—C39	1.353 (11)
C58—C51	1.338 (12)	C38—H38	0.9500
C58—N6	1.345 (10)	C39—C46	1.515 (11)
C58—C59	1.521 (11)	C40—C41	1.549 (13)
C59—N7	1.502 (10)	C40—C42	1.549 (14)
C59—C66	1.524 (11)	C40—H40	1.0000
C59—C60	1.554 (12)	C41—H41A	0.9800
C60—O7	1.228 (9)	C41—H41B	0.9800
C60—N8	1.335 (9)	C41—H41C	0.9800
C61—C62	1.490 (12)	C42—H42A	0.9800
C61—N8	1.514 (10)	C42—H42B	0.9800
C61—H61A	0.9900	C42—H42C	0.9800

C61—H61B	0.9900	C43—C45	1.435 (15)
C62—C63	1.555 (12)	C43—C44	1.586 (16)
C62—H62A	0.9900	C43—H43	1.0000
C62—H62B	0.9900	C44—H44A	0.9800
C63—C64	1.521 (11)	C44—H44B	0.9800
C63—H63A	0.9900	C44—H44C	0.9800
C63—H63B	0.9900	C45—H45A	1.0006
C64—N8	1.481 (10)	C45—H45B	1.0004
C64—C65	1.520 (11)	C45—H45C	1.0006
C64—H64	1.0000	C46—C48	1.510 (11)
C65—O8	1.207 (10)	C46—C47	1.535 (12)
C65—N7	1.359 (10)	C46—H46	1.0000
C66—H66A	0.9800	C47—H47A	0.9800
C66—H66B	0.9800	C47—H47B	0.9800
C66—H66C	0.9800	C47—H47C	0.9800
N2—H2	0.8800	C48—H48A	0.9800
N3—H3A	0.8800	C48—H48B	0.9800
N6—H6	0.8800	C48—H48C	0.9800
N7—H7A	0.8800	S2—O6	1.433 (7)
C1—C6	1.410 (10)	S2—O5	1.446 (7)
C1—C2	1.413 (10)	S2—N5	1.575 (8)
C1—S1	1.811 (7)	N5—C49	1.623 (13)
C2—C3	1.413 (10)	N5—H5A	0.8800
C2—C7	1.520 (11)	C49—C50	1.467 (13)
C3—C4	1.369 (11)	C49—H49A	0.9900
C3—H3	0.9500	C49—H49B	0.9900
C4—C5	1.380 (12)	C50—C51	1.609 (15)
C4—C10	1.524 (12)	C50—H50A	0.9900
C5—C6	1.404 (11)	C50—H50B	0.9900

C20—C19—C24	119.6 (8)	C7—C8—H8A	109.5
C20—C19—C18	133.4 (7)	C7—C8—H8B	109.5
C24—C19—C18	107.0 (7)	H8A—C8—H8B	109.5
C21—C20—C19	119.5 (8)	C7—C8—H8C	109.5
C21—C20—H20	120.2	H8A—C8—H8C	109.5
C19—C20—H20	120.2	H8B—C8—H8C	109.5
C20—C21—C22	120.5 (9)	C7—C9—H9A	109.5
C20—C21—H21	119.7	C7—C9—H9B	109.5
C22—C21—H21	119.8	H9A—C9—H9B	109.5
C21—C22—C23	121.1 (9)	C7—C9—H9C	109.5
C21—C22—H22	119.5	H9A—C9—H9C	109.5
C23—C22—H22	119.4	H9B—C9—H9C	109.5
C24—C23—C22	117.7 (9)	C12—C10—C11	111.9 (9)
C24—C23—H23	121.1	C12—C10—C4	113.9 (10)
C22—C23—H23	121.1	C11—C10—C4	109.5 (9)
C23—C24—N2	131.6 (8)	C12—C10—H10	107.1
C23—C24—C19	121.5 (8)	C11—C10—H10	107.0
N2—C24—C19	106.8 (7)	C4—C10—H10	107.1
N2—C25—C18	108.8 (7)	C10—C11—H11A	109.5
N2—C25—C26	117.5 (7)	C10—C11—H11B	109.5
C18—C25—C26	133.6 (7)	H11A—C11—H11B	109.5
N3—C26—C25	109.2 (6)	C10—C11—H11C	109.5

N3—C26—C27	107.1 (6)	H11A—C11—H11C	109.5
C25—C26—C27	114.3 (6)	H11B—C11—H11C	109.5
N3—C26—C33	108.7 (6)	C10—C12—H12A	109.5
C25—C26—C33	109.5 (6)	C10—C12—H12B	109.5
C27—C26—C33	107.9 (6)	H12A—C12—H12B	109.5
O3—C27—N4	123.2 (7)	C10—C12—H12C	109.5
O3—C27—C26	122.2 (6)	H12A—C12—H12C	109.5
N4—C27—C26	114.6 (6)	H12B—C12—H12C	109.5
N4—C28—C29	102.8 (6)	C6—C13—C15	112.1 (8)
N4—C28—H28A	111.2	C6—C13—C14	111.1 (8)
C29—C28—H28A	111.2	C15—C13—C14	109.8 (7)
N4—C28—H28B	111.2	C6—C13—H13	107.9
C29—C28—H28B	111.2	C15—C13—H13	107.9
H28A—C28—H28B	109.1	C14—C13—H13	107.9
C28—C29—C30	103.4 (6)	C13—C14—H14A	109.5
C28—C29—H29A	111.1	C13—C14—H14B	109.5
C30—C29—H29A	111.1	H14A—C14—H14B	109.5
C28—C29—H29B	111.1	C13—C14—H14C	109.5
C30—C29—H29B	111.1	H14A—C14—H14C	109.5
H29A—C29—H29B	109.0	H14B—C14—H14C	109.5
C29—C30—C31	104.5 (6)	C13—C15—H15A	109.5
C29—C30—H30A	110.8	C13—C15—H15B	109.5
C31—C30—H30A	110.8	H15A—C15—H15B	109.5
C29—C30—H30B	110.9	C13—C15—H15C	109.5
C31—C30—H30B	110.9	H15A—C15—H15C	109.5
H30A—C30—H30B	108.9	H15B—C15—H15C	109.5
N4—C31—C32	111.3 (6)	O2—S1—O1	118.4 (3)
N4—C31—C30	102.5 (6)	O2—S1—N1	109.2 (3)
C32—C31—C30	116.4 (7)	O1—S1—N1	105.4 (3)
N4—C31—H31	108.8	O2—S1—C1	106.7 (3)
C32—C31—H31	108.8	O1—S1—C1	108.1 (3)
C30—C31—H31	108.8	N1—S1—C1	108.9 (4)
O4—C32—N3	123.3 (7)	C16—N1—S1	121.0 (5)
O4—C32—C31	122.1 (7)	C16—N1—H1	119.5
N3—C32—C31	114.5 (7)	S1—N1—H1	119.5
C26—C33—H33A	109.5	N1—C16—C17	112.6 (6)
C26—C33—H33B	109.5	N1—C16—H16A	109.1
H33A—C33—H33B	109.5	C17—C16—H16A	109.1
C26—C33—H33C	109.5	N1—C16—H16B	109.1
H33A—C33—H33C	109.5	C17—C16—H16B	109.1
H33B—C33—H33C	109.5	H16A—C16—H16B	107.8
C57—C52—C51	107.6 (9)	C16—C17—C18	110.0 (6)
C57—C52—C53	118.6 (10)	C16—C17—H17A	109.7
C51—C52—C53	133.8 (9)	C18—C17—H17A	109.7
C54—C53—C52	119.0 (11)	C16—C17—H17B	109.7
C54—C53—H53	120.5	C18—C17—H17B	109.7
C52—C53—H53	120.5	H17A—C17—H17B	108.2
C55—C54—C53	121.0 (12)	C25—C18—C19	106.5 (7)
C55—C54—H54	119.5	C25—C18—C17	131.1 (7)
C53—C54—H54	119.5	C19—C18—C17	122.3 (7)
C54—C55—C56	121.6 (12)	C35—C34—C39	122.4 (7)
C54—C55—H55	119.2	C35—C34—S2	120.4 (6)

C56—C55—H55	119.2	C39—C34—S2	117.1 (5)
C55—C56—C57	115.8 (12)	C34—C35—C36	116.7 (8)
C55—C56—H56	122.1	C34—C35—C40	128.0 (7)
C57—C56—H56	122.1	C36—C35—C40	114.9 (8)
N6—C57—C52	107.5 (8)	C37—C36—C35	122.0 (9)
N6—C57—C56	128.9 (10)	C37—C36—H36	119.0
C52—C57—C56	123.6 (11)	C35—C36—H36	119.0
C51—C58—N6	107.9 (7)	C36—C37—C38	117.7 (8)
C51—C58—C59	133.8 (7)	C36—C37—C43	119.0 (9)
N6—C58—C59	118.2 (7)	C38—C37—C43	123.2 (8)
N7—C59—C58	108.5 (7)	C39—C38—C37	122.4 (8)
N7—C59—C66	109.5 (7)	C39—C38—H38	118.8
C58—C59—C66	110.0 (6)	C37—C38—H38	118.8
N7—C59—C60	105.7 (6)	C38—C39—C34	118.3 (7)
C58—C59—C60	114.4 (7)	C38—C39—C46	115.4 (8)
C66—C59—C60	108.6 (7)	C34—C39—C46	126.3 (7)
O7—C60—N8	126.4 (8)	C35—C40—C41	109.7 (9)
O7—C60—C59	122.1 (7)	C35—C40—C42	112.0 (9)
N8—C60—C59	111.5 (7)	C41—C40—C42	108.1 (9)
C62—C61—N8	102.5 (7)	C35—C40—H40	109.0
C62—C61—H61A	111.3	C41—C40—H40	109.0
N8—C61—H61A	111.3	C42—C40—H40	109.0
C62—C61—H61B	111.3	C40—C41—H41A	109.5
N8—C61—H61B	111.3	C40—C41—H41B	109.5
H61A—C61—H61B	109.2	H41A—C41—H41B	109.5
C61—C62—C63	102.0 (7)	C40—C41—H41C	109.5
C61—C62—H62A	111.4	H41A—C41—H41C	109.5
C63—C62—H62A	111.4	H41B—C41—H41C	109.5
C61—C62—H62B	111.4	C40—C42—H42A	109.5
C63—C62—H62B	111.4	C40—C42—H42B	109.5
H62A—C62—H62B	109.2	H42A—C42—H42B	109.5
C64—C63—C62	104.7 (7)	C40—C42—H42C	109.5
C64—C63—H63A	110.8	H42A—C42—H42C	109.5
C62—C63—H63A	110.8	H42B—C42—H42C	109.5
C64—C63—H63B	110.8	C45—C43—C37	113.5 (10)
C62—C63—H63B	110.8	C45—C43—C44	118.3 (14)
H63A—C63—H63B	108.9	C37—C43—C44	108.2 (11)
N8—C64—C65	109.2 (7)	C45—C43—H43	105.2
N8—C64—C63	102.0 (6)	C37—C43—H43	105.2
C65—C64—C63	115.0 (7)	C44—C43—H43	105.2
N8—C64—H64	110.1	C43—C44—H44A	109.5
C65—C64—H64	110.1	C43—C44—H44B	109.5
C63—C64—H64	110.1	H44A—C44—H44B	109.5
O8—C65—N7	123.3 (8)	C43—C44—H44C	109.5
O8—C65—C64	123.8 (8)	H44A—C44—H44C	109.5
N7—C65—C64	112.8 (7)	H44B—C44—H44C	109.5
C59—C66—H66A	109.5	C43—C45—H45A	111.7
C59—C66—H66B	109.5	C43—C45—H45B	111.6
H66A—C66—H66B	109.5	H45A—C45—H45B	107.2
C59—C66—H66C	109.5	C43—C45—H45C	111.7
H66A—C66—H66C	109.5	H45A—C45—H45C	107.2
H66B—C66—H66C	109.5	H45B—C45—H45C	107.2

C25—N2—C24	110.9 (7)	C48—C46—C39	110.6 (8)
C25—N2—H2	124.5	C48—C46—C47	110.0 (7)
C24—N2—H2	124.5	C39—C46—C47	111.4 (8)
C32—N3—C26	122.5 (6)	C48—C46—H46	108.2
C32—N3—H3A	118.8	C39—C46—H46	108.2
C26—N3—H3A	118.8	C47—C46—H46	108.2
C27—N4—C31	122.3 (6)	C46—C47—H47A	109.5
C27—N4—C28	124.8 (6)	C46—C47—H47B	109.5
C31—N4—C28	112.6 (6)	H47A—C47—H47B	109.5
C57—N6—C58	110.0 (8)	C46—C47—H47C	109.5
C57—N6—H6	125.0	H47A—C47—H47C	109.5
C58—N6—H6	125.0	H47B—C47—H47C	109.5
C65—N7—C59	120.6 (7)	C46—C48—H48A	109.5
C65—N7—H7A	119.7	C46—C48—H48B	109.5
C59—N7—H7A	119.7	H48A—C48—H48B	109.5
C60—N8—C64	123.4 (7)	C46—C48—H48C	109.5
C60—N8—C61	124.4 (7)	H48A—C48—H48C	109.5
C64—N8—C61	111.8 (7)	H48B—C48—H48C	109.5
C6—C1—C2	122.4 (6)	O6—S2—O5	120.5 (6)
C6—C1—S1	120.2 (6)	O6—S2—N5	105.1 (4)
C2—C1—S1	117.4 (6)	O5—S2—N5	108.9 (5)
C3—C2—C1	116.3 (7)	O6—S2—C34	107.0 (4)
C3—C2—C7	116.7 (7)	O5—S2—C34	107.7 (4)
C1—C2—C7	126.9 (7)	N5—S2—C34	107.0 (5)
C4—C3—C2	122.5 (8)	S2—N5—C49	120.7 (6)
C4—C3—H3	118.8	S2—N5—H5A	119.7
C2—C3—H3	118.8	C49—N5—H5A	119.7
C3—C4—C5	119.4 (8)	C50—C49—N5	103.1 (10)
C3—C4—C10	119.2 (8)	C50—C49—H49A	111.1
C5—C4—C10	121.3 (8)	N5—C49—H49A	111.2
C4—C5—C6	122.0 (8)	C50—C49—H49B	111.2
C4—C5—H5	119.0	N5—C49—H49B	111.2
C6—C5—H5	119.0	H49A—C49—H49B	109.1
C5—C6—C1	117.0 (7)	C49—C50—C51	100.0 (10)
C5—C6—C13	114.4 (7)	C49—C50—H50A	111.8
C1—C6—C13	128.5 (7)	C51—C50—H50A	111.8
C8—C7—C9	110.0 (7)	C49—C50—H50B	111.8
C8—C7—C2	112.9 (7)	C51—C50—H50B	111.8
C9—C7—C2	110.0 (7)	H50A—C50—H50B	109.5
C8—C7—H7	107.9	C58—C51—C52	107.0 (8)
C9—C7—H7	107.9	C58—C51—C50	129.4 (9)
C2—C7—H7	107.9	C52—C51—C50	120.6 (9)

C24—C19—C20—C21	1.3 (12)	C62—C61—N8—C64	19.6 (9)
C18—C19—C20—C21	179.1 (8)	C6—C1—C2—C3	6.2 (12)
C19—C20—C21—C22	0.1 (14)	S1—C1—C2—C3	−173.3 (6)
C20—C21—C22—C23	−1.9 (17)	C6—C1—C2—C7	−170.5 (8)
C21—C22—C23—C24	2.3 (16)	S1—C1—C2—C7	9.9 (12)
C22—C23—C24—N2	177.0 (9)	C1—C2—C3—C4	−2.0 (13)
C22—C23—C24—C19	−0.9 (15)	C7—C2—C3—C4	175.1 (9)
C20—C19—C24—C23	−0.9 (14)	C2—C3—C4—C5	−2.5 (15)
C18—C19—C24—C23	−179.2 (8)	C2—C3—C4—C10	179.3 (9)

C20—C19—C24—N2	−179.3 (7)	C3—C4—C5—C6	3.0 (16)
C18—C19—C24—N2	2.4 (9)	C10—C4—C5—C6	−178.9 (10)
N2—C25—C26—N3	46.9 (8)	C4—C5—C6—C1	1.0 (15)
C18—C25—C26—N3	−135.4 (9)	C4—C5—C6—C13	−177.2 (9)
N2—C25—C26—C27	166.8 (6)	C2—C1—C6—C5	−5.8 (13)
C18—C25—C26—C27	−15.5 (12)	S1—C1—C6—C5	173.8 (7)
N2—C25—C26—C33	−72.1 (8)	C2—C1—C6—C13	172.2 (8)
C18—C25—C26—C33	105.7 (10)	S1—C1—C6—C13	−8.3 (13)
N3—C26—C27—O3	−140.1 (7)	C3—C2—C7—C8	71.4 (9)
C25—C26—C27—O3	98.8 (9)	C1—C2—C7—C8	−111.8 (9)
C33—C26—C27—O3	−23.2 (10)	C3—C2—C7—C9	−51.8 (10)
N3—C26—C27—N4	39.0 (8)	C1—C2—C7—C9	124.9 (9)
C25—C26—C27—N4	−82.0 (8)	C3—C4—C10—C12	−59.5 (14)
C33—C26—C27—N4	155.9 (7)	C5—C4—C10—C12	122.4 (12)
N4—C28—C29—C30	−32.1 (8)	C3—C4—C10—C11	66.6 (13)
C28—C29—C30—C31	38.3 (8)	C5—C4—C10—C11	−111.5 (11)
C29—C30—C31—N4	−28.5 (8)	C5—C6—C13—C15	−75.6 (10)
C29—C30—C31—C32	−150.2 (7)	C1—C6—C13—C15	106.4 (11)
N4—C31—C32—O4	−152.9 (7)	C5—C6—C13—C14	47.7 (11)
C30—C31—C32—O4	−35.9 (11)	C1—C6—C13—C14	−130.3 (10)
N4—C31—C32—N3	31.4 (9)	C6—C1—S1—O2	−19.5 (8)
C30—C31—C32—N3	148.3 (7)	C2—C1—S1—O2	160.1 (6)
C57—C52—C53—C54	0 (2)	C6—C1—S1—O1	108.8 (7)
C51—C52—C53—C54	−179.4 (15)	C2—C1—S1—O1	−71.6 (7)
C52—C53—C54—C55	−4 (3)	C6—C1—S1—N1	−137.2 (7)
C53—C54—C55—C56	7 (3)	C2—C1—S1—N1	42.4 (7)
C54—C55—C56—C57	−6 (2)	O2—S1—N1—C16	−36.8 (6)
C51—C52—C57—N6	−1.0 (14)	O1—S1—N1—C16	−164.9 (5)
C53—C52—C57—N6	179.1 (11)	C1—S1—N1—C16	79.4 (6)
C51—C52—C57—C56	−179.7 (12)	S1—N1—C16—C17	95.0 (7)
C53—C52—C57—C56	0 (2)	N1—C16—C17—C18	−165.2 (6)
C55—C56—C57—N6	−176.2 (12)	N2—C25—C18—C19	2.1 (8)
C55—C56—C57—C52	2 (2)	C26—C25—C18—C19	−175.8 (7)
C51—C58—C59—N7	−144.8 (11)	N2—C25—C18—C17	178.4 (7)
N6—C58—C59—N7	39.2 (10)	C26—C25—C18—C17	0.5 (14)
C51—C58—C59—C66	95.4 (13)	C20—C19—C18—C25	179.2 (8)
N6—C58—C59—C66	−80.5 (9)	C24—C19—C18—C25	−2.8 (9)
C51—C58—C59—C60	−27.1 (14)	C20—C19—C18—C17	2.6 (13)
N6—C58—C59—C60	157.0 (7)	C24—C19—C18—C17	−179.4 (7)
N7—C59—C60—O7	−132.1 (8)	C16—C17—C18—C25	−97.6 (9)
C58—C59—C60—O7	108.6 (9)	C16—C17—C18—C19	78.1 (9)
C66—C59—C60—O7	−14.6 (10)	C39—C34—C35—C36	2.4 (14)
N7—C59—C60—N8	46.4 (9)	S2—C34—C35—C36	−173.4 (8)
C58—C59—C60—N8	−72.9 (9)	C39—C34—C35—C40	175.3 (10)
C66—C59—C60—N8	163.8 (7)	S2—C34—C35—C40	−0.6 (15)
N8—C61—C62—C63	−36.1 (8)	C34—C35—C36—C37	−4.1 (16)
C61—C62—C63—C64	41.7 (8)	C40—C35—C36—C37	−177.9 (11)
C62—C63—C64—N8	−28.8 (8)	C35—C36—C37—C38	−0.4 (18)
C62—C63—C64—C65	−146.9 (7)	C35—C36—C37—C43	−177.6 (11)
N8—C64—C65—O8	−144.9 (8)	C36—C37—C38—C39	7.2 (17)
C63—C64—C65—O8	−30.9 (12)	C43—C37—C38—C39	−175.8 (11)
N8—C64—C65—N7	37.2 (9)	C37—C38—C39—C34	−8.8 (16)

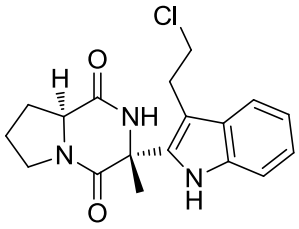
C63—C64—C65—N7	151.2 (7)	C37—C38—C39—C46	172.1 (10)
C18—C25—N2—C24	−0.7 (9)	C35—C34—C39—C38	3.9 (14)
C26—C25—N2—C24	177.6 (6)	S2—C34—C39—C38	179.9 (7)
C23—C24—N2—C25	−179.3 (9)	C35—C34—C39—C46	−177.2 (9)
C19—C24—N2—C25	−1.1 (9)	S2—C34—C39—C46	−1.2 (12)
O4—C32—N3—C26	−163.2 (7)	C34—C35—C40—C41	127.5 (11)
C31—C32—N3—C26	12.6 (10)	C36—C35—C40—C41	−59.5 (13)
C25—C26—N3—C32	75.5 (8)	C34—C35—C40—C42	−112.4 (13)
C27—C26—N3—C32	−48.8 (8)	C36—C35—C40—C42	60.6 (14)
C33—C26—N3—C32	−165.2 (7)	C36—C37—C43—C45	−135.3 (18)
O3—C27—N4—C31	−178.7 (7)	C38—C37—C43—C45	48 (2)
C26—C27—N4—C31	2.2 (10)	C36—C37—C43—C44	91.4 (14)
O3—C27—N4—C28	8.7 (12)	C38—C37—C43—C44	−85.6 (13)
C26—C27—N4—C28	−170.4 (7)	C38—C39—C46—C48	−55.7 (11)
C32—C31—N4—C27	−39.8 (10)	C34—C39—C46—C48	125.4 (9)
C30—C31—N4—C27	−165.0 (7)	C38—C39—C46—C47	67.1 (12)
C32—C31—N4—C28	133.6 (7)	C34—C39—C46—C47	−111.9 (10)
C30—C31—N4—C28	8.4 (8)	C35—C34—S2—O6	118.9 (8)
C29—C28—N4—C27	−171.8 (7)	C39—C34—S2—O6	−57.2 (8)
C29—C28—N4—C31	14.9 (8)	C35—C34—S2—O5	−12.0 (9)
C52—C57—N6—C58	0.7 (12)	C39—C34—S2—O5	171.9 (7)
C56—C57—N6—C58	179.4 (12)	C35—C34—S2—N5	−128.9 (8)
C51—C58—N6—C57	−0.1 (11)	C39—C34—S2—N5	55.0 (8)
C59—C58—N6—C57	176.8 (8)	O6—S2—N5—C49	172.8 (9)
O8—C65—N7—C59	−167.4 (8)	O5—S2—N5—C49	−56.9 (10)
C64—C65—N7—C59	10.5 (10)	C34—S2—N5—C49	59.3 (9)
C58—C59—N7—C65	69.2 (9)	S2—N5—C49—C50	101.7 (10)
C66—C59—N7—C65	−170.8 (7)	N5—C49—C50—C51	−169.2 (8)
C60—C59—N7—C65	−54.0 (9)	N6—C58—C51—C52	−0.5 (12)
O7—C60—N8—C64	178.1 (8)	C59—C58—C51—C52	−176.8 (9)
C59—C60—N8—C64	−0.3 (10)	N6—C58—C51—C50	−160.6 (11)
O7—C60—N8—C61	6.4 (13)	C59—C58—C51—C50	23 (2)
C59—C60—N8—C61	−172.0 (7)	C57—C52—C51—C58	0.9 (14)
C65—C64—N8—C60	−44.2 (10)	C53—C52—C51—C58	−179.2 (15)
C63—C64—N8—C60	−166.4 (7)	C57—C52—C51—C50	163.1 (11)
C65—C64—N8—C61	128.4 (7)	C53—C52—C51—C50	−17 (2)
C63—C64—N8—C61	6.2 (8)	C49—C50—C51—C58	−95.4 (15)
C62—C61—N8—C60	−167.9 (8)	C49—C50—C51—C52	106.8 (13)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5—H5*A*···O3^{i}	0.88	1.95	2.819 (9)	169
N1—H1···O7^{ii}	0.88	1.98	2.850 (8)	171
N7—H7*A*···O6^{iii}	0.88	2.21	2.849 (10)	129
N6—H6···O6^{iii}	0.88	2.41	3.195 (12)	150
N3—H3*A*···O1^{iv}	0.88	2.35	3.002 (8)	131
N2—H2···O1^{iv}	0.88	2.17	3.010 (8)	160

Symmetry codes: (i) *x*+1/2, *y*−1/2, *z*; (ii) *x*−1/2, *y*+1/2, *z*; (iii) *x*, *y*+1, *z*; (iv) *x*, *y*−1, *z*

Appendix 4: Crystallographic data for (3.37)



(**3.37**)

Data obtained at School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

Refinement

The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. H atoms were included in calculated positions with C—H lengths of 0.95(CH), 0.99(CH_2) & 0.98(CH_3)Å; U_{iso}(H) values were fixed at 1.2U_{eq}(C) except for CH_3 where it was 1.5U_{eq}(C).

Experimental:

Crystal data

$C_{18}H_{20}ClN_3O_2$	Z = 3
M_r = 345.82	Mo $K\alpha$ radiation, λ = 0.71073 Å
Trigonal, $P3_1$	μ = 0.24 mm^{-1}
a = 10.1517 (5) Å	T = 100 K
c = 14.5792 (15) Å	0.40 × 0.25 × 0.20 mm
V = 1301.19 (16) $Å^3$	

Data collection

CCD area detector diffractometer	3596 reflections with $I > 2\sigma(I)$
11175 measured reflections	R_{int} = 0.052
4061 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.051	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.096	$\Delta\rho_{max}$ = 0.39 e $Å^{-3}$
S = 1.06	$\Delta\rho_{min}$ = −0.23 e $Å^{-3}$
4061 reflections	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
226 parameters	Flack parameter: 0.04 (6)
1 restraint	

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O2^{i}	0.83 (3)	1.97 (3)	2.744 (3)	154 (3)
N3—H2···O1^{ii}	0.86 (3)	2.09 (3)	2.920 (3)	164 (2)

Data collection: Bruker *SMART*; cell refinement: Bruker *SMART*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

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Supplementary materials

Crystal data

$C_{18}H_{20}ClN_3O_2$	D_x = 1.324 Mg m^{-3}
M_r = 345.82	Mo *K*α radiation, λ = 0.71073 Å
Trigonal, $P3_1$	Cell parameters from 3357 reflections
a = 10.1517 (5) Å	θ = 2.3–26.7°
c = 14.5792 (15) Å	μ = 0.24 mm^{-1}
V = 1301.19 (16) Å^3	*T* = 100 K
Z = 3	Block, White
F(000) = 546	0.40 × 0.25 × 0.20 mm

Data collection

CCD area detector diffractometer	3596 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.052
graphite	θ_{max} = 28.3°, θ_{min} = 2.3°
phi and ω scans	*h* = −13→13
11175 measured reflections	*k* = −13→13
4061 independent reflections	*l* = −19→19

Refinement

Refinement on F^2	Secondary atom site location: Difference Fourier map
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.051$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.096$	$w = 1/[\sigma^2(F_o^2) + (0.0402P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.06$	$(\Delta/\sigma)_{max} < 0.001$
4061 reflections	$\Delta\rho_{max} = 0.39$ e Å^{-3}
226 parameters	$\Delta\rho_{min} = -0.23$ e Å^{-3}
1 restraint	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: Structure-invariant direct methods	Flack parameter: 0.04 (6)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.5339 (3)	0.7628 (3)	0.39334 (16)	0.0168 (5)
C2	0.5516 (3)	0.5470 (3)	0.32764 (16)	0.0179 (5)
C3	0.6388 (3)	0.5557 (3)	0.41355 (16)	0.0202 (5)
H3	0.7473	0.6375	0.4061	0.024*
C4	0.6333 (4)	0.4093 (3)	0.44363 (18)	0.0304 (6)
H4A	0.7178	0.4005	0.4162	0.036*
H4B	0.5355	0.3189	0.4264	0.036*
C5	0.6500 (4)	0.4268 (3)	0.54839 (18)	0.0329 (7)
H5A	0.6119	0.3269	0.5786	0.040*
H5B	0.7575	0.4946	0.5662	0.040*
C6	0.5530 (3)	0.4968 (3)	0.57324 (17)	0.0282 (6)
H6A	0.4452	0.4175	0.5819	0.034*
H6B	0.5905	0.5587	0.6298	0.034*
C7	0.5087 (3)	0.6796 (3)	0.48629 (16)	0.0177 (5)
C8	0.4124 (3)	0.8098 (3)	0.38109 (18)	0.0228 (5)
H8A	0.4294	0.8644	0.3229	0.034*
H8B	0.4192	0.8763	0.4319	0.034*
H8C	0.3111	0.7188	0.3807	0.034*
C9	0.6903 (3)	0.9020 (3)	0.39466 (15)	0.0153 (5)
C10	0.8648 (3)	1.1252 (3)	0.45559 (16)	0.0179 (5)
C11	0.9446 (3)	1.2547 (3)	0.51007 (17)	0.0250 (6)
H11	0.8986	1.2733	0.5614	0.030*

C12	1.0935 (3)	1.3543 (3)	0.48574 (19)	0.0324 (7)
H12	1.1516	1.4439	0.5210	0.039*
C13	1.1608 (3)	1.3257 (3)	0.4098 (2)	0.0306 (6)
H13	1.2639	1.3960	0.3954	0.037*
C14	1.0816 (3)	1.1993 (3)	0.35627 (19)	0.0271 (6)
H14	1.1285	1.1819	0.3049	0.032*
C15	0.9301 (3)	1.0961 (3)	0.37880 (16)	0.0189 (5)
C16	0.8171 (3)	0.9526 (3)	0.34033 (16)	0.0180 (5)
C17	0.8446 (3)	0.8879 (3)	0.25419 (17)	0.0217 (5)
H17A	0.7646	0.7798	0.2483	0.026*
H17B	0.9438	0.8919	0.2592	0.026*
C18	0.8447 (3)	0.9732 (3)	0.16861 (18)	0.0306 (6)
H18A	0.8754	0.9344	0.1153	0.037*
H18B	0.9205	1.0824	0.1759	0.037*
Cl1	0.66151 (8)	0.95295 (8)	0.14665 (5)	0.0393 (2)
N1	0.5136 (2)	0.6550 (2)	0.32064 (14)	0.0171 (4)
N2	0.5718 (2)	0.5929 (2)	0.49233 (13)	0.0198 (4)
N3	0.7196 (2)	1.0053 (2)	0.46458 (14)	0.0184 (4)
O1	0.51990 (19)	0.44961 (19)	0.26851 (11)	0.0230 (4)
O2	0.4367 (2)	0.69384 (19)	0.54976 (12)	0.0241 (4)
H1	0.456 (3)	0.648 (3)	0.2778 (19)	0.023 (7)*
H2	0.656 (3)	1.006 (3)	0.5031 (18)	0.018 (7)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0145 (12)	0.0160 (11)	0.0190 (12)	0.0070 (10)	−0.0011 (9)	−0.0027 (9)
C2	0.0130 (11)	0.0168 (12)	0.0195 (12)	0.0043 (10)	0.0028 (9)	0.0017 (10)
C3	0.0250 (13)	0.0191 (12)	0.0195 (12)	0.0133 (11)	0.0018 (10)	0.0006 (10)
C4	0.0518 (18)	0.0277 (15)	0.0230 (13)	0.0283 (14)	−0.0002 (13)	−0.0017 (11)
C5	0.059 (2)	0.0275 (15)	0.0221 (14)	0.0285 (15)	0.0017 (13)	0.0046 (11)
C6	0.0465 (18)	0.0236 (14)	0.0157 (12)	0.0183 (13)	0.0063 (12)	0.0063 (10)
C7	0.0159 (12)	0.0122 (12)	0.0203 (12)	0.0035 (10)	0.0018 (10)	−0.0027 (9)
C8	0.0182 (13)	0.0244 (13)	0.0287 (14)	0.0128 (11)	−0.0004 (11)	−0.0043 (11)
C9	0.0184 (12)	0.0153 (11)	0.0135 (11)	0.0094 (10)	−0.0003 (9)	0.0021 (9)
C10	0.0141 (11)	0.0164 (12)	0.0195 (11)	0.0048 (10)	0.0012 (9)	0.0023 (9)
C11	0.0257 (14)	0.0183 (13)	0.0253 (14)	0.0067 (11)	−0.0012 (11)	−0.0047 (10)
C12	0.0295 (15)	0.0222 (14)	0.0355 (16)	0.0055 (12)	−0.0027 (12)	−0.0071 (12)
C13	0.0176 (13)	0.0227 (14)	0.0389 (15)	0.0006 (11)	0.0067 (12)	−0.0014 (12)
C14	0.0235 (14)	0.0262 (14)	0.0293 (14)	0.0107 (12)	0.0064 (11)	0.0015 (11)
C15	0.0213 (13)	0.0178 (12)	0.0192 (12)	0.0111 (10)	−0.0006 (10)	0.0000 (9)
C16	0.0190 (12)	0.0144 (12)	0.0201 (12)	0.0081 (10)	0.0007 (10)	0.0033 (9)
C17	0.0183 (12)	0.0195 (12)	0.0232 (13)	0.0063 (11)	0.0052 (10)	−0.0015 (10)
C18	0.0269 (15)	0.0286 (15)	0.0256 (15)	0.0058 (12)	0.0059 (11)	0.0008 (11)
Cl1	0.0339 (4)	0.0356 (4)	0.0306 (4)	0.0040 (3)	−0.0094 (3)	0.0053 (3)
N1	0.0181 (10)	0.0177 (10)	0.0157 (10)	0.0091 (9)	−0.0042 (9)	−0.0015 (8)
N2	0.0256 (11)	0.0206 (11)	0.0153 (10)	0.0131 (10)	0.0053 (9)	0.0022 (8)
N3	0.0160 (10)	0.0189 (11)	0.0186 (10)	0.0075 (9)	0.0034 (9)	−0.0005 (8)
O1	0.0243 (9)	0.0237 (10)	0.0243 (9)	0.0144 (8)	−0.0055 (8)	−0.0085 (7)
O2	0.0269 (10)	0.0193 (9)	0.0235 (9)	0.0096 (8)	0.0078 (8)	0.0002 (7)

Geometric parameters (Å, º)

C1—N1	1.462 (3)	C9—C16	1.373 (3)
C1—C9	1.508 (3)	C9—N3	1.384 (3)
C1—C8	1.539 (3)	C10—N3	1.370 (3)
C1—C7	1.549 (3)	C10—C11	1.397 (3)
C2—O1	1.227 (3)	C10—C15	1.405 (3)
C2—N1	1.336 (3)	C11—C12	1.380 (4)
C2—C3	1.511 (3)	C11—H11	0.9500
C3—N2	1.477 (3)	C12—C13	1.405 (4)
C3—C4	1.524 (3)	C12—H12	0.9500
C3—H3	1.0000	C13—C14	1.368 (4)
C4—C5	1.537 (4)	C13—H13	0.9500
C4—H4A	0.9900	C14—C15	1.400 (4)
C4—H4B	0.9900	C14—H14	0.9500
C5—C6	1.518 (4)	C15—C16	1.443 (3)
C5—H5A	0.9900	C16—C17	1.507 (3)
C5—H5B	0.9900	C17—C18	1.519 (4)
C6—N2	1.482 (3)	C17—H17A	0.9900
C6—H6A	0.9900	C17—H17B	0.9900
C6—H6B	0.9900	C18—Cl1	1.795 (3)
C7—O2	1.232 (3)	C18—H18A	0.9900
C7—N2	1.325 (3)	C18—H18B	0.9900
C8—H8A	0.9800	N1—H1	0.83 (3)
C8—H8B	0.9800	N3—H2	0.86 (3)
C8—H8C	0.9800		

N1—C1—C9	113.49 (19)	N3—C9—C1	116.5 (2)
N1—C1—C8	108.25 (19)	N3—C10—C11	129.9 (2)
C9—C1—C8	110.06 (19)	N3—C10—C15	107.5 (2)
N1—C1—C7	107.61 (18)	C11—C10—C15	122.5 (2)
C9—C1—C7	108.00 (18)	C12—C11—C10	116.8 (2)
C8—C1—C7	109.35 (19)	C12—C11—H11	121.6
O1—C2—N1	122.7 (2)	C10—C11—H11	121.6
O1—C2—C3	122.6 (2)	C11—C12—C13	121.2 (2)
N1—C2—C3	114.6 (2)	C11—C12—H12	119.4
N2—C3—C2	109.16 (19)	C13—C12—H12	119.4
N2—C3—C4	103.23 (19)	C14—C13—C12	121.7 (2)
C2—C3—C4	116.6 (2)	C14—C13—H13	119.2
N2—C3—H3	109.2	C12—C13—H13	119.2
C2—C3—H3	109.2	C13—C14—C15	118.6 (2)
C4—C3—H3	109.2	C13—C14—H14	120.7
C3—C4—C5	103.0 (2)	C15—C14—H14	120.7
C3—C4—H4A	111.2	C14—C15—C10	119.1 (2)
C5—C4—H4A	111.2	C14—C15—C16	133.3 (2)
C3—C4—H4B	111.2	C10—C15—C16	107.5 (2)
C5—C4—H4B	111.2	C9—C16—C15	106.1 (2)
H4A—C4—H4B	109.1	C9—C16—C17	131.4 (2)
C6—C5—C4	103.4 (2)	C15—C16—C17	122.5 (2)
C6—C5—H5A	111.1	C16—C17—C18	112.5 (2)
C4—C5—H5A	111.1	C16—C17—H17A	109.1
C6—C5—H5B	111.1	C18—C17—H17A	109.1
C4—C5—H5B	111.1	C16—C17—H17B	109.1
H5A—C5—H5B	109.1	C18—C17—H17B	109.1

N2—C6—C5	102.61 (19)	H17A—C17—H17B	107.8
N2—C6—H6A	111.2	C17—C18—Cl1	112.11 (18)
C5—C6—H6A	111.2	C17—C18—H18A	109.2
N2—C6—H6B	111.2	Cl1—C18—H18A	109.2
C5—C6—H6B	111.2	C17—C18—H18B	109.2
H6A—C6—H6B	109.2	Cl1—C18—H18B	109.2
O2—C7—N2	122.7 (2)	H18A—C18—H18B	107.9
O2—C7—C1	122.6 (2)	C2—N1—C1	124.7 (2)
N2—C7—C1	114.69 (19)	C2—N1—H1	117.5 (19)
C1—C8—H8A	109.5	C1—N1—H1	116.2 (19)
C1—C8—H8B	109.5	C7—N2—C3	123.75 (19)
H8A—C8—H8B	109.5	C7—N2—C6	123.0 (2)
C1—C8—H8C	109.5	C3—N2—C6	112.00 (19)
H8A—C8—H8C	109.5	C10—N3—C9	109.3 (2)
H8B—C8—H8C	109.5	C10—N3—H2	122.5 (17)
C16—C9—N3	109.6 (2)	C9—N3—H2	127.5 (18)
C16—C9—C1	134.0 (2)		

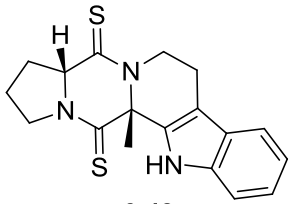
O1—C2—C3—N2	−139.7 (2)	N3—C9—C16—C15	−0.6 (3)
N1—C2—C3—N2	41.2 (3)	C1—C9—C16—C15	179.7 (2)
O1—C2—C3—C4	−23.3 (3)	N3—C9—C16—C17	−177.4 (2)
N1—C2—C3—C4	157.6 (2)	C1—C9—C16—C17	2.9 (4)
N2—C3—C4—C5	−30.7 (3)	C14—C15—C16—C9	177.7 (3)
C2—C3—C4—C5	−150.4 (2)	C10—C15—C16—C9	0.0 (3)
C3—C4—C5—C6	40.2 (3)	C14—C15—C16—C17	−5.1 (4)
C4—C5—C6—N2	−33.1 (3)	C10—C15—C16—C17	177.2 (2)
N1—C1—C7—O2	−138.3 (2)	C9—C16—C17—C18	104.0 (3)
C9—C1—C7—O2	98.8 (3)	C15—C16—C17—C18	−72.4 (3)
C8—C1—C7—O2	−20.9 (3)	C16—C17—C18—Cl1	−65.6 (2)
N1—C1—C7—N2	42.2 (2)	O1—C2—N1—C1	173.0 (2)
C9—C1—C7—N2	−80.7 (2)	C3—C2—N1—C1	−7.9 (3)
C8—C1—C7—N2	159.6 (2)	C9—C1—N1—C2	85.5 (3)
N1—C1—C9—C16	2.7 (4)	C8—C1—N1—C2	−152.1 (2)
C8—C1—C9—C16	−118.7 (3)	C7—C1—N1—C2	−34.0 (3)
C7—C1—C9—C16	122.0 (3)	O2—C7—N2—C3	170.6 (2)
N1—C1—C9—N3	−177.0 (2)	C1—C7—N2—C3	−9.9 (3)
C8—C1—C9—N3	61.6 (3)	O2—C7—N2—C6	4.4 (4)
C7—C1—C9—N3	−57.7 (3)	C1—C7—N2—C6	−176.2 (2)
N3—C10—C11—C12	177.5 (3)	C2—C3—N2—C7	−32.5 (3)
C15—C10—C11—C12	−0.6 (4)	C4—C3—N2—C7	−157.1 (2)
C10—C11—C12—C13	−0.2 (4)	C2—C3—N2—C6	135.1 (2)
C11—C12—C13—C14	0.8 (5)	C4—C3—N2—C6	10.5 (3)
C12—C13—C14—C15	−0.5 (4)	C5—C6—N2—C7	−177.9 (2)
C13—C14—C15—C10	−0.3 (4)	C5—C6—N2—C3	14.4 (3)
C13—C14—C15—C16	−177.8 (3)	C11—C10—N3—C9	−179.2 (3)
N3—C10—C15—C14	−177.6 (2)	C15—C10—N3—C9	−0.9 (3)
C11—C10—C15—C14	0.9 (4)	C16—C9—N3—C10	0.9 (3)
N3—C10—C15—C16	0.5 (3)	C1—C9—N3—C10	−179.3 (2)
C11—C10—C15—C16	179.0 (2)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O2^{i}	0.83 (3)	1.97 (3)	2.744 (3)	154 (3)
N3—H2···O1^{ii}	0.86 (3)	2.09 (3)	2.920 (3)	164 (2)

Symmetry codes: (i) −*x*+*y*, −*x*+1, *z*−1/3; (ii) −*y*+1, *x*−*y*+1, *z*+1/3.

Appendix 5: Crystallographic data for (3.48)



(**3.48**)

Data obtained at School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

Refinement

The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. H atoms were included in calculated positions with C—H lengths of 0.95(CH), 0.99(CH_2) & 0.98(CH_3)Å; U_{iso}(H) values were fixed at 1.2U_{eq}(C) except for CH_3 where it was 1.5U_{eq}(C).

Experimental:

Crystal data

$C_{18}H_{19}N_3S_2$	V = 815.9 (2) Å^3
M_r = 341.48	Z = 2
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 8.8373 (14) Å	μ = 0.33 mm^{-1}
b = 10.6736 (17) Å	T = 100 K
c = 9.0407 (14) Å	0.30 × 0.20 × 0.04 mm
β = 106.912 (3)°	

Data collection

CCD area detector diffractometer	2190 reflections with $I > 2\sigma(I)$
7109 measured reflections	R_{int} = 0.050
3709 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.054	$\Delta\rho_{max}$ = 0.42 e Å^{-3}
S = 0.66	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
3709 reflections	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
213 parameters	Flack parameter: −0.03 (6)
1 restraint	

Table 1
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3···S1^{i}	0.97 (2)	2.61 (3)	3.438 (3)	143 (2)
N3—H3···S2	0.97 (2)	2.51 (3)	3.069 (3)	116.4 (19)

Data collection: Bruker *SMART*; cell refinement: Bruker *SMART*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

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Supplementary materials

Crystal data

$C_{18}H_{19}N_3S_2$	$F(000) = 360$
$M_r = 341.48$	$D_x = 1.390$ Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 8.8373$ (14) Å	Cell parameters from 1031 reflections
$b = 10.6736$ (17) Å	$\theta = 2.4$–$21.3°$
$c = 9.0407$ (14) Å	$\mu = 0.33$ mm^{-1}
$\beta = 106.912$ (3)°	$T = 100$ K
$V = 815.9$ (2) Å^3	Plate, White
$Z = 2$	0.30 × 0.20 × 0.04 mm

Data collection

CCD area detector diffractometer	2190 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.050$
graphite	$\theta_{max} = 28.3°$, $\theta_{min} = 2.4°$
phi and ω scans	$h = -11 \rightarrow 11$
7109 measured reflections	$k = -14 \rightarrow 14$
3709 independent reflections	$l = -11 \rightarrow 11$

Refinement

Refinement on F^2	Secondary atom site location: Difference Fourier map
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.041$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.054$	$w = 1/[\sigma^2(F_o^2) + (0.P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 0.66$	$(\Delta/\sigma)_{max} < 0.001$
3709 reflections	$\Delta\rho_{max} = 0.42$ e Å^{-3}
213 parameters	$\Delta\rho_{min} = -0.27$ e Å^{-3}
1 restraint	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: Structure-invariant direct methods	Flack parameter: −0.03 (6)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.4095 (3)	1.2172 (2)	0.8080 (3)	0.0263 (8)
H1A	0.4735	1.2707	0.7598	0.032*
H1B	0.4671	1.2063	0.9189	0.032*
C2	0.2466 (3)	1.2753 (3)	0.7885 (3)	0.0366 (8)
H2A	0.2231	1.3400	0.7066	0.044*
H2B	0.2411	1.3139	0.8863	0.044*
C3	0.1298 (3)	1.1649 (3)	0.7429 (3)	0.0300 (8)
H3A	0.1193	1.1202	0.8353	0.036*
H3B	0.0241	1.1938	0.6803	0.036*
C4	0.2070 (3)	1.0818 (3)	0.6479 (3)	0.0253 (8)
H4	0.1863	1.1193	0.5425	0.030*
C5	0.1533 (3)	0.9476 (3)	0.6302 (3)	0.0209 (7)
C6	0.2186 (3)	0.7259 (2)	0.6265 (3)	0.0238 (8)
H6A	0.2393	0.6934	0.5317	0.029*
H6B	0.1041	0.7171	0.6144	0.029*
C7	0.3121 (3)	0.6501 (2)	0.7650 (3)	0.0213 (7)
H7A	0.2842	0.6759	0.8589	0.026*
H7B	0.2885	0.5597	0.7472	0.026*
C8	0.4836 (3)	0.6745 (3)	0.7845 (3)	0.0183 (7)
C9	0.6181 (3)	0.5953 (3)	0.8394 (3)	0.0193 (7)

C10	0.6439 (3)	0.4783 (2)	0.9123 (3)	0.0215 (7)
H10	0.5606	0.4368	0.9394	0.026*
C11	0.7913 (3)	0.4236 (3)	0.9445 (3)	0.0265 (7)
H11	0.8086	0.3434	0.9920	0.032*
C12	0.9155 (3)	0.4848 (3)	0.9082 (3)	0.0306 (8)
H12	1.0159	0.4451	0.9310	0.037*
C13	0.8957 (3)	0.6023 (3)	0.8396 (3)	0.0313 (8)
H13	0.9808	0.6448	0.8170	0.038*
C14	0.7455 (3)	0.6550 (3)	0.8052 (3)	0.0233 (7)
C15	0.5320 (3)	0.7786 (3)	0.7243 (3)	0.0194 (7)
C16	0.4328 (3)	0.8890 (3)	0.6487 (3)	0.0198 (7)
C17	0.4897 (3)	1.0114 (3)	0.7353 (3)	0.0204 (7)
C18	0.4350 (3)	0.9059 (3)	0.4796 (3)	0.0265 (7)
H18A	0.5430	0.9248	0.4777	0.040*
H18B	0.3647	0.9750	0.4320	0.040*
H18C	0.3987	0.8285	0.4218	0.040*
N1	0.3773 (3)	1.0953 (2)	0.7297 (2)	0.0218 (6)
N2	0.2635 (3)	0.8598 (2)	0.6465 (2)	0.0197 (6)
N3	0.6894 (3)	0.7671 (2)	0.7290 (3)	0.0242 (6)
S1	−0.04099 (8)	0.92311 (7)	0.58844 (9)	0.0299 (2)
S2	0.67853 (9)	1.04361 (8)	0.81851 (9)	0.0359 (2)
H3	0.756 (3)	0.839 (2)	0.725 (3)	0.046 (10)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.037 (2)	0.0223 (18)	0.0189 (18)	−0.0107 (16)	0.0064 (16)	−0.0035 (14)
C2	0.044 (2)	0.027 (2)	0.0308 (19)	0.0047 (17)	−0.0020 (17)	0.0005 (16)
C3	0.0287 (18)	0.0282 (18)	0.0295 (19)	0.0072 (15)	0.0030 (15)	0.0022 (15)
C4	0.0318 (19)	0.0226 (19)	0.0184 (17)	0.0015 (14)	0.0021 (15)	0.0071 (14)
C5	0.0279 (18)	0.024 (2)	0.0109 (14)	0.0019 (14)	0.0053 (13)	0.0016 (14)
C6	0.0203 (18)	0.0239 (19)	0.025 (2)	−0.0112 (14)	0.0027 (15)	−0.0060 (15)
C7	0.0240 (17)	0.0142 (16)	0.0244 (18)	0.0004 (13)	0.0049 (14)	0.0000 (14)
C8	0.0190 (17)	0.0226 (17)	0.0146 (16)	−0.0052 (14)	0.0070 (13)	−0.0073 (14)
C9	0.0228 (17)	0.0229 (17)	0.0122 (15)	−0.0006 (14)	0.0053 (13)	−0.0057 (14)
C10	0.0234 (17)	0.0250 (18)	0.0163 (16)	−0.0051 (14)	0.0060 (13)	−0.0085 (14)
C11	0.0354 (18)	0.0198 (16)	0.0222 (17)	0.0025 (17)	0.0052 (14)	−0.0033 (15)
C12	0.0250 (19)	0.035 (2)	0.0302 (19)	0.0078 (16)	0.0061 (15)	−0.0030 (16)
C13	0.0246 (19)	0.042 (2)	0.0290 (19)	−0.0021 (16)	0.0108 (15)	−0.0035 (17)
C14	0.0176 (17)	0.034 (2)	0.0163 (17)	−0.0022 (15)	0.0027 (14)	−0.0020 (15)
C15	0.0187 (17)	0.0244 (18)	0.0151 (16)	0.0000 (15)	0.0049 (13)	−0.0029 (14)
C16	0.0170 (16)	0.0242 (18)	0.0180 (16)	−0.0040 (13)	0.0051 (13)	−0.0001 (14)
C17	0.0253 (17)	0.023 (2)	0.0174 (16)	−0.0069 (15)	0.0131 (14)	−0.0010 (14)
C18	0.0354 (17)	0.0244 (18)	0.0222 (16)	−0.0040 (16)	0.0125 (14)	0.0006 (14)
N1	0.0281 (15)	0.0183 (14)	0.0179 (14)	−0.0071 (12)	0.0049 (12)	0.0019 (12)
N2	0.0205 (14)	0.0228 (15)	0.0151 (13)	−0.0039 (11)	0.0044 (11)	−0.0012 (11)
N3	0.0191 (15)	0.0288 (16)	0.0268 (15)	−0.0036 (13)	0.0098 (12)	0.0034 (13)
S1	0.0212 (4)	0.0355 (5)	0.0325 (5)	0.0000 (4)	0.0071 (4)	0.0037 (4)
S2	0.0244 (5)	0.0378 (5)	0.0462 (5)	−0.0088 (4)	0.0115 (4)	−0.0158 (5)

Geometric parameters (Å, º)

C1—N1	1.469 (3)	C8—C9	1.424 (3)
C1—C2	1.529 (3)	C9—C10	1.400 (3)
C1—H1A	0.9900	C9—C14	1.404 (3)
C1—H1B	0.9900	C10—C11	1.379 (3)
C2—C3	1.541 (4)	C10—H10	0.9500
C2—H2A	0.9900	C11—C12	1.396 (4)
C2—H2B	0.9900	C11—H11	0.9500
C3—C4	1.527 (4)	C12—C13	1.387 (4)
C3—H3A	0.9900	C12—H12	0.9500
C3—H3B	0.9900	C13—C14	1.391 (4)
C4—N1	1.478 (3)	C13—H13	0.9500
C4—C5	1.503 (3)	C14—N3	1.398 (3)
C4—H4	1.0000	C15—N3	1.385 (3)
C5—N2	1.328 (3)	C15—C16	1.509 (3)
C5—S1	1.668 (3)	C16—N2	1.523 (3)
C6—N2	1.480 (3)	C16—C17	1.531 (4)
C6—C7	1.518 (3)	C16—C18	1.545 (3)
C6—H6A	0.9900	C17—N1	1.327 (3)
C6—H6B	0.9900	C17—S2	1.655 (3)
C7—C8	1.497 (3)	C18—H18A	0.9800
C7—H7A	0.9900	C18—H18B	0.9800
C7—H7B	0.9900	C18—H18C	0.9800
C8—C15	1.360 (3)	N3—H3	0.97 (2)

N1—C1—C2	105.1 (2)	C14—C9—C8	107.2 (3)
N1—C1—H1A	110.7	C11—C10—C9	119.5 (3)
C2—C1—H1A	110.7	C11—C10—H10	120.3
N1—C1—H1B	110.7	C9—C10—H10	120.3
C2—C1—H1B	110.7	C10—C11—C12	120.7 (3)
H1A—C1—H1B	108.8	C10—C11—H11	119.6
C1—C2—C3	104.8 (2)	C12—C11—H11	119.6
C1—C2—H2A	110.8	C13—C12—C11	121.5 (3)
C3—C2—H2A	110.8	C13—C12—H12	119.2
C1—C2—H2B	110.8	C11—C12—H12	119.2
C3—C2—H2B	110.8	C12—C13—C14	117.0 (3)
H2A—C2—H2B	108.9	C12—C13—H13	121.5
C4—C3—C2	102.7 (2)	C14—C13—H13	121.5
C4—C3—H3A	111.2	C13—C14—N3	129.4 (3)
C2—C3—H3A	111.2	C13—C14—C9	122.8 (3)
C4—C3—H3B	111.2	N3—C14—C9	107.7 (2)
C2—C3—H3B	111.2	C8—C15—N3	110.3 (2)
H3A—C3—H3B	109.1	C8—C15—C16	127.6 (2)
N1—C4—C5	113.0 (2)	N3—C15—C16	121.9 (2)
N1—C4—C3	102.6 (2)	C15—C16—N2	106.6 (2)
C5—C4—C3	115.8 (2)	C15—C16—C17	112.0 (2)
N1—C4—H4	108.4	N2—C16—C17	110.9 (2)
C5—C4—H4	108.4	C15—C16—C18	111.5 (2)
C3—C4—H4	108.4	N2—C16—C18	107.8 (2)
N2—C5—C4	117.5 (2)	C17—C16—C18	108.1 (2)
N2—C5—S1	126.0 (2)	N1—C17—C16	115.2 (2)
C4—C5—S1	116.5 (2)	N1—C17—S2	121.4 (2)
N2—C6—C7	110.6 (2)	C16—C17—S2	123.2 (2)

N2—C6—H6A	109.5	C16—C18—H18A	109.5
C7—C6—H6A	109.5	C16—C18—H18B	109.5
N2—C6—H6B	109.5	H18A—C18—H18B	109.5
C7—C6—H6B	109.5	C16—C18—H18C	109.5
H6A—C6—H6B	108.1	H18A—C18—H18C	109.5
C8—C7—C6	107.1 (2)	H18B—C18—H18C	109.5
C8—C7—H7A	110.3	C17—N1—C1	122.8 (2)
C6—C7—H7A	110.3	C17—N1—C4	126.5 (2)
C8—C7—H7B	110.3	C1—N1—C4	110.7 (2)
C6—C7—H7B	110.3	C5—N2—C6	120.4 (2)
H7A—C7—H7B	108.6	C5—N2—C16	122.9 (2)
C15—C8—C9	107.2 (2)	C6—N2—C16	115.3 (2)
C15—C8—C7	121.4 (2)	C15—N3—C14	107.4 (2)
C9—C8—C7	130.6 (2)	C15—N3—H3	122.9 (16)
C10—C9—C14	118.5 (3)	C14—N3—H3	124.1 (15)
C10—C9—C8	134.3 (3)		

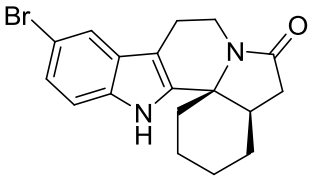
N1—C1—C2—C3	17.0 (3)	C8—C15—C16—C18	−119.6 (3)
C1—C2—C3—C4	−33.5 (3)	N3—C15—C16—C18	54.8 (3)
C2—C3—C4—N1	36.8 (3)	C15—C16—C17—N1	−148.4 (2)
C2—C3—C4—C5	160.3 (2)	N2—C16—C17—N1	−29.5 (3)
N1—C4—C5—N2	−18.7 (3)	C18—C16—C17—N1	88.4 (3)
C3—C4—C5—N2	−136.6 (2)	C15—C16—C17—S2	36.4 (3)
N1—C4—C5—S1	162.46 (18)	N2—C16—C17—S2	155.30 (18)
C3—C4—C5—S1	44.5 (3)	C18—C16—C17—S2	−86.7 (3)
N2—C6—C7—C8	−55.1 (3)	C16—C17—N1—C1	179.0 (2)
C6—C7—C8—C15	21.3 (3)	S2—C17—N1—C1	−5.7 (3)
C6—C7—C8—C9	−147.4 (3)	C16—C17—N1—C4	−0.7 (4)
C15—C8—C9—C10	179.6 (3)	S2—C17—N1—C4	174.5 (2)
C7—C8—C9—C10	−10.5 (5)	C2—C1—N1—C17	−173.0 (2)
C15—C8—C9—C14	−1.6 (3)	C2—C1—N1—C4	6.8 (3)
C7—C8—C9—C14	168.3 (3)	C5—C4—N1—C17	26.6 (4)
C14—C9—C10—C11	−1.8 (4)	C3—C4—N1—C17	152.0 (2)
C8—C9—C10—C11	176.9 (3)	C5—C4—N1—C1	−153.1 (2)
C9—C10—C11—C12	1.4 (4)	C3—C4—N1—C1	−27.8 (3)
C10—C11—C12—C13	0.3 (4)	C4—C5—N2—C6	−178.4 (2)
C11—C12—C13—C14	−1.5 (4)	S1—C5—N2—C6	0.4 (4)
C12—C13—C14—N3	−175.9 (3)	C4—C5—N2—C16	−12.9 (4)
C12—C13—C14—C9	1.0 (4)	S1—C5—N2—C16	165.8 (2)
C10—C9—C14—C13	0.6 (4)	C7—C6—N2—C5	−127.8 (3)
C8—C9—C14—C13	−178.4 (3)	C7—C6—N2—C16	65.7 (3)
C10—C9—C14—N3	178.1 (2)	C15—C16—N2—C5	160.1 (2)
C8—C9—C14—N3	−0.9 (3)	C17—C16—N2—C5	38.0 (3)
C9—C8—C15—N3	3.6 (3)	C18—C16—N2—C5	−80.1 (3)
C7—C8—C15—N3	−167.4 (2)	C15—C16—N2—C6	−33.7 (3)
C9—C8—C15—C16	178.6 (2)	C17—C16—N2—C6	−155.8 (2)
C7—C8—C15—C16	7.5 (4)	C18—C16—N2—C6	86.1 (3)
C8—C15—C16—N2	−2.2 (4)	C8—C15—N3—C14	−4.2 (3)
N3—C15—C16—N2	172.3 (2)	C16—C15—N3—C14	−179.5 (2)
C8—C15—C16—C17	119.2 (3)	C13—C14—N3—C15	−179.6 (3)
N3—C15—C16—C17	−66.3 (3)	C9—C14—N3—C15	3.1 (3)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3···S1^{i}	0.97 (2)	2.61 (3)	3.438 (3)	143 (2)
N3—H3···S2	0.97 (2)	2.51 (3)	3.069 (3)	116.4 (19)

Symmetry code: (i) *x*+1, *y*, *z*.

Appendix 6: Crystallographic data for (4.164)



(**4.164**)

Data obtained Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA

Experimental:

Crystal data

$C_{18}H_{19}BrN_2O$	V = 1591.39 (8) Å^3
M_r = 359.27	Z = 4
Monoclinic, $C2$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 18.7232 (4) Å	μ = 2.59 mm^{-1}
b = 6.9539 (2) Å	T = 150 K
c = 14.1450 (4) Å	0.17 × 0.06 × 0.05 mm
β = 120.2197 (13)°	

Data collection

Area diffractometer	3391 independent reflections
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	2808 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.80, T_{max} = 0.89	R_{int} = 0.068
7601 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039	No H atoms present
$wR(F^2)$ = 0.081	$\Delta\rho_{max}$ = 0.70 e Å^{-3}
S = 0.93	$\Delta\rho_{min}$ = −1.07 e Å^{-3}
3391 reflections	Absolute structure: Flack (1983), 0 Friedel-pairs
200 parameters	Flack parameter: −0.030 (11)
1 restraint	

Table 1
Selected geometric parameters (Å, º)

Br1—C2	1.907 (3)	C11—C12	1.532 (5)
C2—C3	1.405 (5)	C12—N13	1.455 (4)
C2—C10	1.368 (5)	N13—C14	1.484 (4)
C3—C4	1.383 (5)	N13—C17	1.364 (5)

C4—C5	1.395 (5)	C14—C15	1.566 (5)
C5—N6	1.383 (5)	C14—C19	1.530 (5)
C5—C9	1.408 (5)	C15—C16	1.525 (5)
N6—C7	1.377 (4)	C15—C1	1.543 (5)
C7—C8	1.377 (5)	C16—C17	1.518 (5)
C7—C14	1.506 (5)	C17—O18	1.230 (4)
C8—C9	1.445 (5)	C19—C20	1.530 (4)
C8—C11	1.500 (5)	C20—C21	1.519 (5)
C9—C10	1.401 (5)	C21—C1	1.521 (5)

Br1—C2—C3	117.8 (3)	C12—N13—C14	117.5 (3)
Br1—C2—C10	119.1 (3)	C12—N13—C17	119.3 (3)
C3—C2—C10	123.1 (3)	C14—N13—C17	111.1 (3)
C2—C3—C4	119.7 (3)	C7—C14—N13	104.5 (3)
C3—C4—C5	118.0 (3)	C7—C14—C15	113.7 (3)
C4—C5—N6	130.1 (3)	N13—C14—C15	101.1 (3)
C4—C5—C9	121.8 (3)	C7—C14—C19	109.6 (3)
N6—C5—C9	108.1 (3)	N13—C14—C19	113.6 (3)
C5—N6—C7	108.4 (3)	C15—C14—C19	113.8 (3)
N6—C7—C8	110.4 (3)	C14—C15—C16	101.6 (3)
N6—C7—C14	125.3 (3)	C14—C15—C1	111.8 (3)
C8—C7—C14	124.3 (3)	C16—C15—C1	109.6 (3)
C7—C8—C9	106.1 (3)	C15—C16—C17	104.1 (3)
C7—C8—C11	124.1 (3)	C16—C17—N13	108.6 (3)
C9—C8—C11	129.9 (3)	C16—C17—O18	126.1 (4)
C8—C9—C5	107.0 (3)	N13—C17—O18	125.2 (4)
C8—C9—C10	133.2 (3)	C14—C19—C20	114.7 (3)
C5—C9—C10	119.7 (3)	C19—C20—C21	109.8 (3)
C9—C10—C2	117.7 (3)	C20—C21—C1	110.2 (3)
C8—C11—C12	110.3 (3)	C15—C1—C21	114.3 (3)
C11—C12—N13	111.0 (3)		

Table 2
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H61···O18^{i}	0.87	1.98	2.838 (6)	171

Symmetry code: (i) *x*, *y*+1, *z*.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

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Supplementary materials

(7t)

Crystal data

$C_{18}H_{19}BrN_2O$	$F(000)$ = 736
M_r = 359.27	D_x = 1.499 Mg m^{-3}
Monoclinic, *C*2	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: C 2y	Cell parameters from 1825 reflections
a = 18.7232 (4) Å	θ = 5–27°
b = 6.9539 (2) Å	μ = 2.59 mm^{-1}
c = 14.1450 (4) Å	*T* = 150 K
β = 120.2197 (13)°	Plate, Colourless
V = 1591.39 (8) Å^3	0.17 × 0.06 × 0.05 mm
Z = 4	

Data collection

Area diffractometer	2808 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.068
ω scans	θ_{max} = 27.5°, θ_{min} = 5.4°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	*h* = −23→24
T_{min} = 0.80, T_{max} = 0.89	*k* = −9→8
7601 measured reflections	*l* = −18→18
3391 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Inferred from neighbouring sites
Least-squares matrix: Full	No H atoms present
$R[F^2 > 2\sigma(F^2)]$ = 0.039	Method = Modified Sheldrick *w* = $1/[\sigma^2(F^2) + (0.02P)^2 + 2.8P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2)$ = 0.081	$(\Delta/\sigma)_{max}$ = 0.002
S = 0.93	$\Delta\rho_{max}$ = 0.70 e Å^{-3}
3391 reflections	$\Delta\rho_{min}$ = −1.07 e Å^{-3}
200 parameters	Absolute structure: Flack (1983), 0 Friedel-pairs
1 restraint	Flack parameter: −0.030 (11)
Primary atom site location: Structure-invariant direct methods	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

H-atom positions were not refined or were subject to contraints(Warning: _refine_ls_hydrogen_treatment reports none)

The following H sites were not refined or were subject to constraints:

H61, H12, H11, H212, H211, H202, H201, H192, H191, H162, H161, H151, H122, H121, H112, H111, H101, H41, H31

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.54156 (2)	0.17418 (13)	0.90615 (3)	0.0346
C2	0.49056 (19)	0.2133 (5)	0.7522 (3)	0.0225
C3	0.5049 (2)	0.3891 (5)	0.7156 (3)	0.0263
C4	0.4657 (2)	0.4278 (5)	0.6047 (3)	0.0262
C5	0.4124 (2)	0.2886 (5)	0.5327 (3)	0.0212
N6	0.36376 (19)	0.2918 (4)	0.4200 (3)	0.0223
C7	0.3211 (2)	0.1207 (5)	0.3862 (3)	0.0191
C8	0.3403 (2)	0.0051 (5)	0.4749 (3)	0.0187
C9	0.3998 (2)	0.1112 (5)	0.5702 (3)	0.0183
C10	0.4400 (2)	0.0734 (5)	0.6827 (3)	0.0219
C11	0.3018 (2)	−0.1877 (5)	0.4672 (3)	0.0237
C12	0.2318 (2)	−0.2248 (5)	0.3499 (3)	0.0235
N13	0.25123 (18)	−0.1432 (4)	0.2708 (2)	0.0184
C14	0.2592 (2)	0.0691 (5)	0.2696 (3)	0.0181
C15	0.2929 (2)	0.0929 (5)	0.1890 (3)	0.0212
C16	0.3487 (2)	−0.0830 (5)	0.2168 (3)	0.0231
C17	0.3079 (3)	−0.2327 (6)	0.2523 (4)	0.0215
O18	0.3257 (2)	−0.4046 (4)	0.2678 (3)	0.0311
C19	0.17817 (17)	0.1764 (8)	0.2337 (2)	0.0238
C20	0.1126 (2)	0.1505 (8)	0.1131 (3)	0.0317
C21	0.1482 (2)	0.2061 (7)	0.0413 (3)	0.0328
C1	0.2230 (2)	0.0820 (5)	0.0684 (3)	0.0258
H31	0.5404	0.4772	0.7662	0.0318*
H41	0.4741	0.5425	0.5790	0.0313*
H101	0.4328	−0.0424	0.7095	0.0251*
H111	0.3447	−0.2846	0.4879	0.0291*
H112	0.2801	−0.1916	0.5165	0.0289*
H121	0.2247	−0.3644	0.3409	0.0291*
H122	0.1810	−0.1646	0.3384	0.0285*
H151	0.3235	0.2133	0.2032	0.0254*
H161	0.4030	−0.0511	0.2794	0.0285*
H162	0.3538	−0.1269	0.1559	0.0283*
H191	0.1917	0.3125	0.2449	0.0285*
H192	0.1552	0.1372	0.2792	0.0282*
H201	0.0653	0.2300	0.0964	0.0384*
H202	0.0960	0.0153	0.1014	0.0379*
H211	0.1632	0.3441	0.0514	0.0402*
H212	0.1091	0.1870	−0.0337	0.0398*
H11	0.2479	0.1208	0.0239	0.0316*
H12	0.2047	−0.0520	0.0528	0.0304*
H61	0.3580	0.3881	0.3778	0.0288*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.0356 (2)	0.0425 (2)	0.01935 (16)	0.0064 (3)	0.00907 (13)	0.0002 (2)
C2	0.0151 (15)	0.032 (3)	0.0172 (15)	0.0063 (15)	0.0059 (13)	−0.0006 (15)
C3	0.0196 (18)	0.030 (2)	0.0248 (19)	−0.0037 (16)	0.0080 (16)	−0.0085 (16)
C4	0.028 (2)	0.0220 (19)	0.030 (2)	−0.0043 (15)	0.0156 (18)	−0.0019 (16)
C5	0.0197 (19)	0.023 (2)	0.0187 (19)	−0.0031 (15)	0.0075 (16)	−0.0015 (15)
N6	0.0235 (17)	0.0188 (16)	0.0240 (16)	−0.0024 (13)	0.0116 (14)	0.0031 (13)
C7	0.0195 (17)	0.019 (2)	0.0210 (17)	0.0011 (13)	0.0114 (15)	−0.0010 (13)
C8	0.0202 (18)	0.0135 (17)	0.0211 (17)	−0.0011 (14)	0.0094 (15)	−0.0008 (14)
C9	0.0180 (16)	0.0167 (18)	0.0212 (18)	0.0032 (12)	0.0107 (15)	−0.0015 (13)
C10	0.0216 (18)	0.0260 (19)	0.0222 (18)	0.0065 (15)	0.0140 (16)	0.0042 (15)
C11	0.030 (2)	0.0200 (19)	0.0248 (19)	−0.0041 (15)	0.0164 (17)	0.0038 (15)
C12	0.0240 (19)	0.0215 (19)	0.029 (2)	−0.0028 (15)	0.0169 (17)	0.0009 (16)
N13	0.0246 (15)	0.0129 (14)	0.0223 (15)	−0.0022 (12)	0.0153 (13)	0.0006 (12)
C14	0.0160 (16)	0.0185 (18)	0.0182 (17)	−0.0020 (14)	0.0075 (14)	−0.0024 (14)
C15	0.0306 (19)	0.0162 (16)	0.0238 (18)	−0.0007 (14)	0.0190 (16)	0.0047 (14)
C16	0.0233 (19)	0.0218 (19)	0.0271 (19)	0.0034 (15)	0.0149 (16)	0.0036 (16)
C17	0.024 (2)	0.021 (2)	0.020 (2)	0.0033 (16)	0.0119 (17)	0.0037 (16)
O18	0.0460 (19)	0.0197 (15)	0.0359 (18)	0.0087 (13)	0.0267 (16)	0.0076 (13)
C19	0.0212 (15)	0.0242 (16)	0.0240 (15)	0.002 (2)	0.0099 (12)	0.002 (2)
C20	0.0196 (16)	0.039 (3)	0.0285 (18)	0.008 (2)	0.0062 (14)	0.000 (2)
C21	0.037 (2)	0.032 (3)	0.0207 (16)	0.0038 (18)	0.0087 (15)	0.0040 (18)
C1	0.028 (2)	0.0254 (19)	0.0218 (19)	−0.0007 (16)	0.0112 (16)	0.0005 (15)

Geometric parameters (Å, º)

Br1—C2	1.907 (3)	N13—C14	1.484 (4)
C2—C3	1.405 (5)	N13—C17	1.364 (5)
C2—C10	1.368 (5)	C14—C15	1.566 (5)
C3—C4	1.383 (5)	C14—C19	1.530 (5)
C3—H31	0.922	C15—C16	1.525 (5)
C4—C5	1.395 (5)	C15—C1	1.543 (5)
C4—H41	0.923	C15—H151	0.977
C5—N6	1.383 (5)	C16—C17	1.518 (5)
C5—C9	1.408 (5)	C16—H161	0.981
N6—C7	1.377 (4)	C16—H162	0.964
N6—H61	0.867	C17—O18	1.230 (4)
C7—C8	1.377 (5)	C19—C20	1.530 (4)
C7—C14	1.506 (5)	C19—H191	0.972
C8—C9	1.445 (5)	C19—H192	0.976
C8—C11	1.500 (5)	C20—C21	1.519 (5)
C9—C10	1.401 (5)	C20—H201	0.966
C10—H101	0.929	C20—H202	0.978
C11—C12	1.532 (5)	C21—C1	1.521 (5)
C11—H111	0.974	C21—H211	0.990
C11—H112	0.969	C21—H212	0.947
C12—N13	1.455 (4)	C1—H11	0.992
C12—H121	0.979	C1—H12	0.978
C12—H122	0.975		

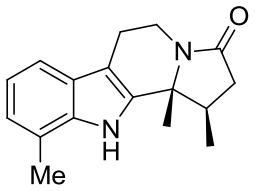
Br1—C2—C3	117.8 (3)	N13—C14—C15	101.1 (3)
Br1—C2—C10	119.1 (3)	C7—C14—C19	109.6 (3)
C3—C2—C10	123.1 (3)	N13—C14—C19	113.6 (3)
C2—C3—C4	119.7 (3)	C15—C14—C19	113.8 (3)
C2—C3—H31	119.3	C14—C15—C16	101.6 (3)
C4—C3—H31	121.0	C14—C15—C1	111.8 (3)
C3—C4—C5	118.0 (3)	C16—C15—C1	109.6 (3)
C3—C4—H41	121.1	C14—C15—H151	110.5
C5—C4—H41	120.9	C16—C15—H151	112.3
C4—C5—N6	130.1 (3)	C1—C15—H151	110.7
C4—C5—C9	121.8 (3)	C15—C16—C17	104.1 (3)
N6—C5—C9	108.1 (3)	C15—C16—H161	108.4
C5—N6—C7	108.4 (3)	C17—C16—H161	108.8
C5—N6—H61	126.0	C15—C16—H162	112.7
C7—N6—H61	125.4	C17—C16—H162	111.8
N6—C7—C8	110.4 (3)	H161—C16—H162	110.7
N6—C7—C14	125.3 (3)	C16—C17—N13	108.6 (3)
C8—C7—C14	124.3 (3)	C16—C17—O18	126.1 (4)
C7—C8—C9	106.1 (3)	N13—C17—O18	125.2 (4)
C7—C8—C11	124.1 (3)	C14—C19—C20	114.7 (3)
C9—C8—C11	129.9 (3)	C14—C19—H191	106.7
C8—C9—C5	107.0 (3)	C20—C19—H191	107.0
C8—C9—C10	133.2 (3)	C14—C19—H192	109.7
C5—C9—C10	119.7 (3)	C20—C19—H192	109.3
C9—C10—C2	117.7 (3)	H191—C19—H192	109.3
C9—C10—H101	121.4	C19—C20—C21	109.8 (3)
C2—C10—H101	120.9	C19—C20—H201	109.1
C8—C11—C12	110.3 (3)	C21—C20—H201	110.3
C8—C11—H111	107.7	C19—C20—H202	108.1
C12—C11—H111	109.6	C21—C20—H202	109.9
C8—C11—H112	109.4	H201—C20—H202	109.5
C12—C11—H112	109.5	C20—C21—C1	110.2 (3)
H111—C11—H112	110.3	C20—C21—H211	109.8
C11—C12—N13	111.0 (3)	C1—C21—H211	110.9
C11—C12—H121	107.1	C20—C21—H212	111.2
N13—C12—H121	110.9	C1—C21—H212	107.3
C11—C12—H122	109.9	H211—C21—H212	107.5
N13—C12—H122	107.8	C15—C1—C21	114.3 (3)
H121—C12—H122	110.2	C15—C1—H11	106.3
C12—N13—C14	117.5 (3)	C21—C1—H11	110.7
C12—N13—C17	119.3 (3)	C15—C1—H12	107.6
C14—N13—C17	111.1 (3)	C21—C1—H12	108.1
C7—C14—N13	104.5 (3)	H11—C1—H12	109.8
C7—C14—C15	113.7 (3)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H61···O18^{i}	0.87	1.98	2.838 (6)	171

Symmetry code: (i) *x*, *y*+1, *z*.

Appendix 7: Crystallographic data for (4.167)



(**4.167**)

Data obtained at Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA

Experimental:

Crystal data

$C_{17}H_{20}N_2O$	V = 1448.31 (5) Å^3
M_r = 268.36	Z = 4
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 5.7927 (1) Å	μ = 0.08 mm^{-1}
b = 12.1783 (2) Å	T = 150 K
c = 20.5935 (5) Å	0.20 × 0.18 × 0.05 mm
β = 94.4916 (8)°	

Data collection

Area diffractometer	3315 independent reflections
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	2036 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.94, T_{max} = 1.00	R_{int} = 0.041
24984 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.055	0 restraints
$wR(F^2)$ = 0.189	No H atoms present
S = 0.99	$\Delta\rho_{max}$ = 0.45 e Å^{-3}
3315 reflections	$\Delta\rho_{min}$ = −0.43 e Å^{-3}
181 parameters	

Table 1
Selected geometric parameters (Å, º)

O1—C2	1.240 (3)	C8—C10	1.559 (3)
C2—N3	1.340 (3)	C10—C11	1.532 (3)
C2—C11	1.504 (3)	C10—C12	1.519 (3)
N3—C4	1.462 (3)	N13—C14	1.385 (3)
N3—C8	1.480 (3)	C14—C15	1.416 (3)
C4—C5	1.525 (4)	C14—C19	1.398 (3)

C5—C6	1.502 (3)	C15—C16	1.407 (4)
C6—C7	1.365 (3)	C16—C17	1.384 (4)
C6—C15	1.430 (3)	C17—C18	1.402 (4)
C7—C8	1.505 (3)	C18—C19	1.388 (4)
C7—N13	1.385 (3)	C19—C20	1.498 (4)
C8—C9	1.530 (3)		

O1—C2—N3	125.3 (2)	C9—C8—C10	112.2 (2)
O1—C2—C11	126.8 (2)	C8—C10—C11	102.08 (18)
N3—C2—C11	107.9 (2)	C8—C10—C12	117.0 (2)
C2—N3—C4	124.1 (2)	C11—C10—C12	114.1 (2)
C2—N3—C8	113.82 (19)	C10—C11—C2	104.04 (19)
C4—N3—C8	122.08 (19)	C7—N13—C14	108.31 (19)
N3—C4—C5	109.7 (2)	N13—C14—C15	107.3 (2)
C4—C5—C6	108.6 (2)	N13—C14—C19	129.6 (2)
C5—C6—C7	123.6 (2)	C15—C14—C19	123.0 (2)
C5—C6—C15	129.5 (2)	C6—C15—C14	107.4 (2)
C7—C6—C15	106.7 (2)	C6—C15—C16	133.5 (2)
C6—C7—C8	125.5 (2)	C14—C15—C16	119.1 (2)
C6—C7—N13	110.2 (2)	C15—C16—C17	118.5 (3)
C8—C7—N13	124.3 (2)	C16—C17—C18	120.9 (3)
C7—C8—N3	106.45 (18)	C17—C18—C19	122.8 (3)
C7—C8—C9	111.31 (19)	C14—C19—C18	115.7 (2)
N3—C8—C9	110.32 (18)	C14—C19—C20	122.7 (2)
C7—C8—C10	115.39 (19)	C18—C19—C20	121.5 (2)
N3—C8—C10	100.42 (18)		

Table 2
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H41···C14^{i}	0.99	2.57	3.521 (4)	161
C12—H122···O1^{ii}	0.97	2.55	3.395 (4)	146
N13—H131···O1^{ii}	0.88	1.97	2.851 (4)	178

Symmetry codes: (i) *x*+1, *y*, *z*; (ii) −*x*+3/2, *y*+1/2, −*z*+1/2.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

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Supplementary materials

(7t)

Crystal data

$C_{17}H_{20}N_2O$	$F(000)$ = 576
M_r = 268.36	D_x = 1.231 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 3455 reflections
a = 5.7927 (1) Å	θ = 5–27°
b = 12.1783 (2) Å	μ = 0.08 mm^{-1}
c = 20.5935 (5) Å	T = 150 K
β = 94.4916 (8)°	Plate, Colourless
V = 1448.31 (5) Å^3	0.20 × 0.18 × 0.05 mm
Z = 4	

Data collection

Area diffractometer	2036 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.041
ω scans	θ_{max} = 27.5°, θ_{min} = 5.1°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	h = −7→7
T_{min} = 0.94, T_{max} = 1.00	k = −15→15
24984 measured reflections	l = −26→26
3315 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.055	No H atoms present
	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)]
$wR(F^2)$ = 0.189	where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 16.1 25.4

14.0 5.09 0.777

S = 0.99
3315 reflections
181 parameters
0 restraints

$(\Delta/\sigma)_{max}$ = 0.0002
$\Delta\rho_{max}$ = 0.45 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

H-atom positions were not refined or were subject to contraints(Warning: _refine_ls_hydrogen_treatment reports none)

The following H sites were not refined or were subject to constraints:

H131, H201, H203, H202, H181, H171, H161, H121, H122, H123, H112, H111, H101, H93, H92, H91, H52, H51, H42, H41

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	1.1138 (3)	0.45198 (14)	0.23180 (9)	0.0345
C2	0.9784 (4)	0.52985 (19)	0.23688 (12)	0.0289
N3	0.9728 (3)	0.59531 (16)	0.28904 (10)	0.0281
C4	1.1118 (4)	0.5776 (2)	0.35052 (12)	0.0325
C5	0.9529 (5)	0.5593 (2)	0.40517 (13)	0.0372
C6	0.7670 (4)	0.6455 (2)	0.40027 (12)	0.0307
C7	0.7077 (4)	0.70408 (18)	0.34494 (11)	0.0267
C8	0.8047 (4)	0.68664 (19)	0.28007 (11)	0.0265
C9	0.9248 (4)	0.7902 (2)	0.25753 (13)	0.0327
C10	0.6324 (4)	0.6378 (2)	0.22569 (11)	0.0286
C11	0.7922 (4)	0.5675 (2)	0.18683 (12)	0.0313
C12	0.4848 (4)	0.7187 (2)	0.18452 (13)	0.0381
N13	0.5468 (3)	0.78416 (17)	0.35712 (9)	0.0279
C14	0.4964 (4)	0.7754 (2)	0.42158 (11)	0.0293
C15	0.6315 (4)	0.6881 (2)	0.44966 (12)	0.0323
C16	0.6077 (5)	0.6590 (3)	0.51490 (13)	0.0440
C17	0.4493 (5)	0.7158 (3)	0.54896 (13)	0.0484
C18	0.3179 (5)	0.8016 (3)	0.51951 (13)	0.0456
C19	0.3379 (5)	0.8344 (2)	0.45567 (12)	0.0356
C20	0.1948 (6)	0.9264 (3)	0.42557 (14)	0.0510
H41	1.2116	0.6425	0.3605	0.0388*
H42	1.2087	0.5125	0.3457	0.0386*
H51	1.0435	0.5652	0.4480	0.0452*
H52	0.8857	0.4854	0.4009	0.0451*
H91	0.8125	0.8501	0.2533	0.0488*
H92	1.0527	0.8103	0.2894	0.0485*
H93	0.9871	0.7777	0.2152	0.0478*
H101	0.5275	0.5877	0.2471	0.0337*
H111	0.8605	0.6134	0.1538	0.0381*
H112	0.7113	0.5049	0.1653	0.0383*
H123	0.3744	0.6779	0.1548	0.0570*
H122	0.3988	0.7663	0.2115	0.0564*
H121	0.5827	0.7638	0.1584	0.0567*
H161	0.6976	0.6006	0.5354	0.0532*
H171	0.4297	0.6965	0.5929	0.0583*
H181	0.2085	0.8388	0.5440	0.0552*

H202	0.1089	0.9642	0.4563	0.0782*
H203	0.2890	0.9783	0.4062	0.0789*
H201	0.0915	0.8999	0.3911	0.0788*
H131	0.4945	0.8356	0.3296	0.0346*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0344 (9)	0.0303 (9)	0.0388 (10)	0.0032 (7)	0.0028 (7)	−0.0067 (7)
C2	0.0281 (11)	0.0273 (11)	0.0315 (12)	−0.0020 (9)	0.0046 (9)	−0.0033 (9)
N3	0.0258 (9)	0.0287 (10)	0.0296 (10)	0.0018 (8)	0.0009 (7)	−0.0019 (8)
C4	0.0281 (11)	0.0387 (13)	0.0302 (12)	0.0041 (10)	−0.0008 (9)	−0.0032 (10)
C5	0.0402 (14)	0.0407 (14)	0.0309 (13)	0.0102 (11)	0.0033 (10)	0.0024 (11)
C6	0.0311 (12)	0.0334 (12)	0.0280 (11)	0.0049 (10)	0.0041 (9)	0.0007 (9)
C7	0.0271 (10)	0.0258 (11)	0.0274 (11)	0.0023 (9)	0.0028 (8)	−0.0016 (9)
C8	0.0240 (10)	0.0294 (11)	0.0261 (11)	0.0017 (9)	0.0029 (8)	−0.0007 (9)
C9	0.0302 (12)	0.0311 (12)	0.0375 (13)	−0.0018 (10)	0.0080 (10)	−0.0009 (10)
C10	0.0258 (11)	0.0328 (12)	0.0271 (11)	−0.0012 (9)	0.0024 (8)	−0.0012 (9)
C11	0.0313 (12)	0.0317 (12)	0.0307 (12)	−0.0007 (10)	0.0015 (9)	−0.0033 (10)
C12	0.0325 (13)	0.0470 (15)	0.0342 (13)	0.0079 (11)	−0.0007 (10)	−0.0012 (12)
N13	0.0294 (10)	0.0291 (10)	0.0256 (10)	0.0027 (8)	0.0037 (7)	0.0016 (8)
C14	0.0306 (11)	0.0310 (12)	0.0262 (11)	0.0004 (10)	0.0016 (9)	−0.0035 (9)
C15	0.0336 (12)	0.0375 (13)	0.0259 (12)	0.0033 (10)	0.0028 (9)	0.0001 (10)
C16	0.0530 (17)	0.0540 (17)	0.0255 (12)	0.0138 (14)	0.0052 (11)	0.0048 (12)
C17	0.0567 (17)	0.0648 (19)	0.0250 (12)	0.0160 (15)	0.0099 (12)	0.0028 (13)
C18	0.0466 (15)	0.0613 (19)	0.0298 (13)	0.0153 (14)	0.0083 (11)	−0.0047 (12)
C19	0.0361 (13)	0.0420 (14)	0.0292 (12)	0.0073 (11)	0.0046 (10)	−0.0037 (11)
C20	0.0604 (19)	0.0584 (19)	0.0349 (14)	0.0274 (16)	0.0086 (13)	−0.0007 (13)

Geometric parameters (Å, º)

O1—C2	1.240 (3)	C10—H101	0.988
C2—N3	1.340 (3)	C11—H111	0.986
C2—C11	1.504 (3)	C11—H112	0.982
N3—C4	1.462 (3)	C12—H123	0.984
N3—C8	1.480 (3)	C12—H122	0.968
C4—C5	1.525 (4)	C12—H121	0.980
C4—H41	0.991	N13—C14	1.385 (3)
C4—H42	0.981	N13—H131	0.882
C5—C6	1.502 (3)	C14—C15	1.416 (3)
C5—H51	0.993	C14—C19	1.398 (3)
C5—H52	0.981	C15—C16	1.407 (4)
C6—C7	1.365 (3)	C16—C17	1.384 (4)
C6—C15	1.430 (3)	C16—H161	0.959
C7—C8	1.505 (3)	C17—C18	1.402 (4)
C7—N13	1.385 (3)	C17—H171	0.951
C8—C9	1.530 (3)	C18—C19	1.388 (4)
C8—C10	1.559 (3)	C18—H181	0.954
C9—H91	0.977	C19—C20	1.498 (4)
C9—H92	0.981	C20—H202	0.953
C9—H93	0.981	C20—H203	0.944
C10—C11	1.532 (3)	C20—H201	0.949

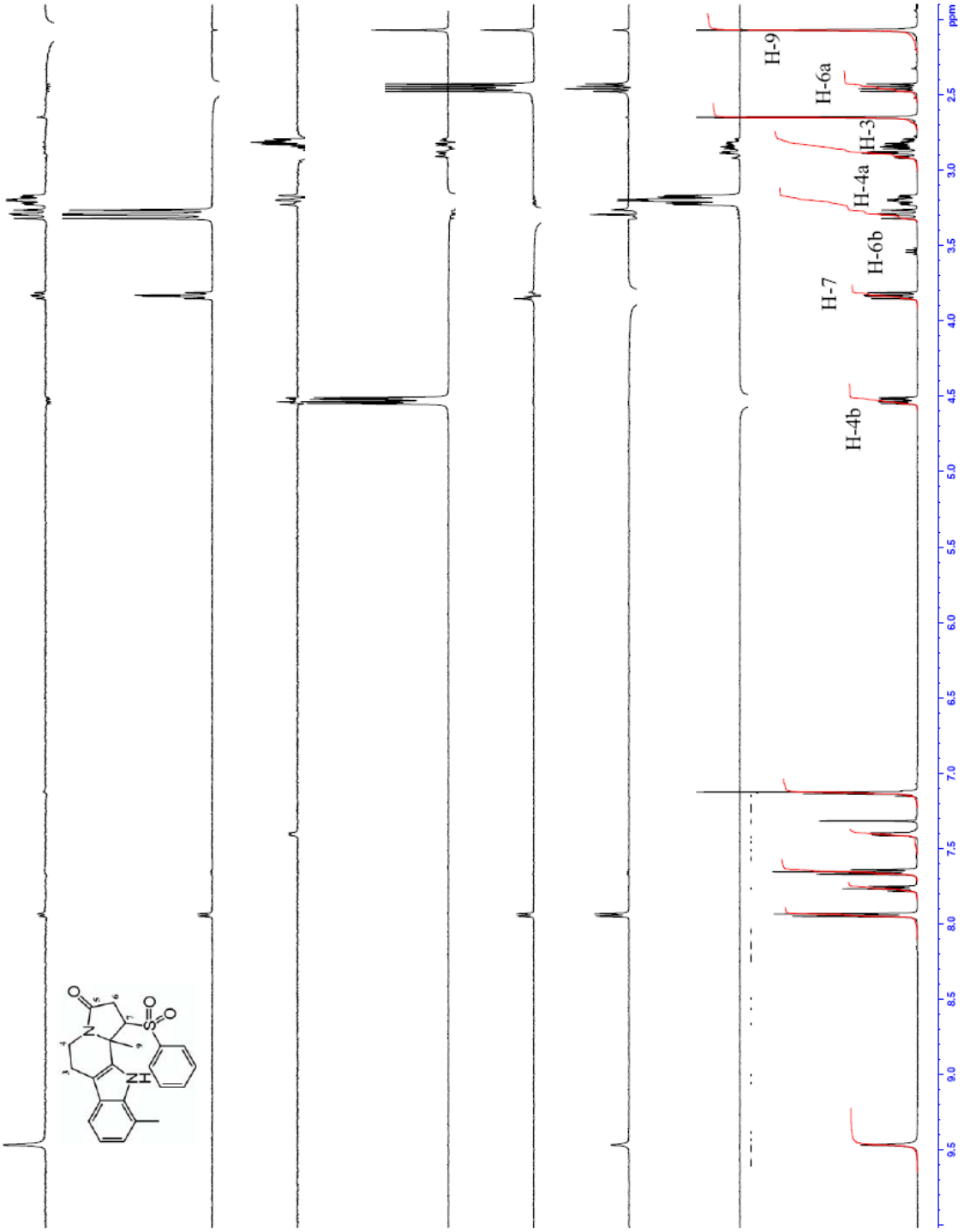
C10—C12	1.519 (3)		
O1—C2—N3	125.3 (2)	C12—C10—H101	108.1
O1—C2—C11	126.8 (2)	C10—C11—C2	104.04 (19)
N3—C2—C11	107.9 (2)	C10—C11—H111	109.6
C2—N3—C4	124.1 (2)	C2—C11—H111	109.9
C2—N3—C8	113.82 (19)	C10—C11—H112	112.5
C4—N3—C8	122.08 (19)	C2—C11—H112	111.3
N3—C4—C5	109.7 (2)	H111—C11—H112	109.4
N3—C4—H41	109.6	C10—C12—H123	109.2
C5—C4—H41	109.8	C10—C12—H122	111.2
N3—C4—H42	108.2	H123—C12—H122	108.7
C5—C4—H42	109.9	C10—C12—H121	110.2
H41—C4—H42	109.7	H123—C12—H121	108.5
C4—C5—C6	108.6 (2)	H122—C12—H121	109.0
C4—C5—H51	109.7	C7—N13—C14	108.31 (19)
C6—C5—H51	109.6	C7—N13—H131	125.8
C4—C5—H52	109.1	C14—N13—H131	125.7
C6—C5—H52	110.9	N13—C14—C15	107.3 (2)
H51—C5—H52	108.9	N13—C14—C19	129.6 (2)
C5—C6—C7	123.6 (2)	C15—C14—C19	123.0 (2)
C5—C6—C15	129.5 (2)	C6—C15—C14	107.4 (2)
C7—C6—C15	106.7 (2)	C6—C15—C16	133.5 (2)
C6—C7—C8	125.5 (2)	C14—C15—C16	119.1 (2)
C6—C7—N13	110.2 (2)	C15—C16—C17	118.5 (3)
C8—C7—N13	124.3 (2)	C15—C16—H161	121.0
C7—C8—N3	106.45 (18)	C17—C16—H161	120.5
C7—C8—C9	111.31 (19)	C16—C17—C18	120.9 (3)
N3—C8—C9	110.32 (18)	C16—C17—H171	119.5
C7—C8—C10	115.39 (19)	C18—C17—H171	119.7
N3—C8—C10	100.42 (18)	C17—C18—C19	122.8 (3)
C9—C8—C10	112.2 (2)	C17—C18—H181	119.1
C8—C9—H91	109.1	C19—C18—H181	118.1
C8—C9—H92	109.8	C14—C19—C18	115.7 (2)
H91—C9—H92	109.6	C14—C19—C20	122.7 (2)
C8—C9—H93	110.4	C18—C19—C20	121.5 (2)
H91—C9—H93	109.1	C19—C20—H202	112.8
H92—C9—H93	108.8	C19—C20—H203	110.9
C8—C10—C11	102.08 (18)	H202—C20—H203	107.8
C8—C10—C12	117.0 (2)	C19—C20—H201	110.6
C11—C10—C12	114.1 (2)	H202—C20—H201	109.3
C8—C10—H101	107.3	H203—C20—H201	105.2
C11—C10—H101	107.8		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H41···C14^{i}	0.99	2.57	3.521 (4)	161
C12—H122···O1^{ii}	0.97	2.55	3.395 (4)	146
N13—H131···O1^{ii}	0.88	1.97	2.851 (4)	178

Symmetry codes: (i) *x*+1, *y*, *z*; (ii) −*x*+3/2, *y*+1/2, −*z*+1/2.

Appendix 8: NOE data for (4.121)



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